FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE MEETING

Friday, May 2, 2014

8:00 a.m. to 3:58 p.m.

Hilton Washington DC North/Gaithersburg

The Ballrooms

620 Perry Parkway

Gaithersburg, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Kalyani Bhatt, BS, MS

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Ralph B. D'Agostino, Sr., PhD

Professor of Mathematics and Statistics, Biostatistics and Epidemiology

Executive Director MA/PhD Program in Biostatistics

Director, Statistics and Consulting Unit

Boston University

Boston, Massachusetts

Lorraine J. Gudas, PhD
Chairman, Department of Pharmacology
Professor of Pharmacology, Medicine
and Urology
Weill Cornell Medical College
New York, New York

Judith M. Kramer, MD, MS
Professor Emerita of Medicine
Duke University School of Medicine
Durham, North Carolina

Ruth M. Parker, MD
(Acting Chairperson)
Professor of Medicine, Pediatrics and Public Health
Emory University School of Medicine
Atlanta, Georgia

Paul Pisarik, MD, MPH, FAAFP
Vohra Wound Physicians
Owasso, Oklahoma

Estela M. Pledge, MS, LCPC, MAC, ACS

(Consumer Representative)

Health Education Specialist, Alcohol and Other Drug Resource Center – Beu Health Center

Western Illinois University

Macomb, Illinois

Maria C. Pruchnicki, PharmD, BCPS, CLS

Associate Professor of Clinical Pharmacy

Division of Pharmacy Practice and Administration

College of Pharmacy

The Ohio State University

Columbus, Ohio

Christianne L. Roumie, MD, MPH

Assistant Professor

Internal Medicine and Pediatrics

Institute for Medicine and Public Health Vanderbilt University

Staff Physician

Department of Veterans Affairs

Tennessee Valley Healthcare System

Nashville, Tennessee

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE MEMBER

(Non-Voting)

Lorna C. Totman, PhD, DABT

(Industry Representative)

Lorna Totman Consulting, LLC

Annandale, Virginia

TEMPORARY MEMBERS (Voting)

Tobias Gerhard, PhD, RPh

Assistant Professor

Rutgers University, Ernest Mario School of Pharmacy

New Brunswick, New Jersey

Dennis R. Ownby, MD

Professor of Pediatrics

Division of Allergy, Immunology, and Rheumatology

Georgia Regents University

Augusta, Georgia

Thomas D. Platts-Mills, PhD

Director, Asthma and Allergic Disease Center

University of Virginia Medical School

Charlottesville, Virginia

Tish Simon

(Patient Representative)

Jackson, New Jersey

Kelly Dean Stone, MD, PhD

Director, Allergy and Immunology Clinical

Fellowship Program

National Institutes of Allergy and Infectious

Diseases, National Institutes of Health (NIH)

Bethesda, Maryland

Kenneth Towbin, MD

Chief, Clinical Child & Adolescent Psychiatry

National Institutes of Health (NIH)

Bethesda, Maryland

James M. Tracy, DO

Assistant Clinical Professor of Medicine

Department of Internal Medicine

Division of Allergy and Immunology Creighton

University School of Medicine

Omaha, Nebraska

FDA PARTICIPANTS (Non-Voting)

Sandra Kweder, MD, FACP

RADM (retired), U.S. Public Health Service

Director (Acting)

Office of Drug Evaluation IV (ODE IV)

Deputy Director, Office of New Drugs (OND)

CDER, FDA

Theresa M. Michele, MD

Director

Division of Nonprescription Clinical Evaluation

(DNCE), ODE IV, OND, CDER, FDA

Lucie Yang, MD

Team Leader

DNCE, ODE IV, OND, CDER, FDA

Mary Parks, MD

Deputy Director

Office of Drug Evaluation II (ODE II)

OND, CDER, FDA

Badrul Chowdhury, MD, PhD

Director

Division of Pulmonary, Allergy, and Rheumatology

Products (DPARP)

ODE II, OND, CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:01 a.m.)

Call to Order

Introduction of Committee

DR. PARKER: Good morning. All right. We're going to try that one more time. Good morning.

(Chorus of good mornings.)

DR. PARKER: Thank you. Here we go. We'll start so that we can finish. How about that?

I'd first like to remind everybody to please silence their cell phones, smartphones, other devices, if you've not already done so. I'd also like to identify the FDA press contact, Andrea Fischer, who is waving at us all. Thank you very much.

I am Ruth Parker, and I am the acting chair of the meeting today. We will begin by asking all the members, consultants, the FDA panel, and the DFO to go around the table and state their name into the record, if you will. Make sure that your microphone is on when we do that. We'll start here

with Dr. Totman. Thank you.

DR. TOTMAN: Good morning. I'm Lorna Totman, the industry representative to NDAC.

DR. TRACY: Dr. James Tracy from Creighton University.

DR. STONE: Kelly Stone, National Institute of Allergy and Infectious Diseases.

MS. SIMON: Tish Simon, patient advisory representative for the FDA.

DR. TOWBIN: Kenneth Towbin from the intramural program of the National Institute of Mental Health and the Pediatric Advisory Committee.

DR. PLATTS-MILLS: I'm Tom Platts-Mills from the University of Virginia.

DR. OWNBY: Dennis Ownby from Georgia Regents University.

DR. GERHARD: Tobias Gerhard, Rutgers University.

DR. PRUCHNICKI: Maria Pruchnicki, The Ohio State University.

MS. BHATT: Good morning. I'm Kalyani Bhatt. I'm the designated federal official with

the advisory committee and consultant management.

DR. KRAMER: Judith Kramer, emerita professor, Duke University.

MS. PLEDGE: Estela Pledge, Western Illinois University, Macomb, Illinois. I'm the consumer representative.

DR. GUDAS: Lorraine Gudas, Weill Cornell Medical College.

DR. PISARIK: Paul Pisarik, family physician, Owasso, Oklahoma.

DR. D'AGOSTINO: Ralph D'Agostino from Boston University.

DR. YANG: Lucie Yang, FDA, Division of Nonprescription Clinical Evaluation.

DR. MICHELE: Theresa Michele, Division of Nonprescription Clinical Evaluation.

DR. CHOWDHURY: I'm Badrul Chowdhury, Division of Pulmonary, Allergy Rheumatology Products, FDA.

DR. PARKS: Mary Parks, deputy director, Office of Drug Evaluation II.

DR. PARKER: For topics such as those being

discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topics at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you

very much.

Now, I'll pass it to Kalyani Bhatt, who will read the Conflict of Interest Statement for us.

DR. BHATT: Good morning. Before I start the Conflict of Interest Statement, Dr. Roumie, could you please introduce yourself for the record and where you're from?

DR. ROUMIE: Dr. Christianne Roumie. I'm an internist and a pediatrician. I do cardiovascular pharmacoepidemiology. Thank you.

Conflict of Interest Statement

DR. BHATT: The Food and Drug Administration is convening today's meeting of the Nonprescription Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of

the committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 USC Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 USC Section 208, their employers. This

interest may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves a discussion of data submitted by MSD Consumer Care, Incorporated to support a new drug application, 204804, for over-the-counter, OTC, marketing of montelukast 10 milligram tablets, proposed trade name Singulair Allergy. The proposed OTC use is temporarily relieves these symptoms due to hay fever or other upper respiratory allergies: nasal congestion, runny nose, itchy, water eyes, sneezing, itching of the nose.

The applicant proposed to label the product for OTC use in adults 18 years and older. Efficacy and safety data, as well as results of consumer studies, will be discussed. The committee will be asked to consider whether the data support an acceptable risk/benefit profile for the nonprescription use of montelukast tablets by OTC consumers.

This a particular matters meeting during which specific matters related to MSD Consumer Care's NDA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue. With respect to FDA's invited industry rep, we would like to disclose that Dr. Lorna Totman is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Totman's role at this meeting is to represent industry in general and not any particular company. Dr. Totman is an independent pharmaceutical consultant.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on

the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. PARKER: We will now proceed with Dr. Michele's introductory remarks.

FDA Introductory Remarks - Theresa Michele

DR. MICHELE: Good morning, Dr. Parker. Good morning, members of the Nonprescription Drugs Advisory Committee, guest members, representatives from Merck, and also members of the public. My name is Terri Michele, and I am the division director of the Division of Nonprescription Clinical Evaluation, as well as a practicing pulmonologist. On behalf of the division and all of us here at FDA, it is my pleasure to welcome you to the Washington area.

Today we are here to discuss the new drug

application for montelukast for over-the-counter treatment of adults with allergic rhinitis. Before we get started, I want to thank all of the members of the committee who have taken time out of their busy schedules to thoughtfully review the background package and to be here today.

Although this is an NDAC meeting, we have a number of guest members supplementing our committee, and that includes members of the Pulmonary Allergy Drugs Advisory Committee, the Psychopharmacologic Drugs Advisory Committee, and the Drugs Safety and Risk Management Advisory Committee. As members of the advisory committee, you provide important, expert, scientific advice that is taken very seriously by the FDA.

Last, but certainly not least, I would like to thank those members of the public, including representatives from various professional societies, as well as consumer groups, who have taken the effort to be here today to present your views. I'd also like to thank those of you who have provided written feedback. Your input is

extremely valuable, both to the deliberations of the committee, as well as to the FDA.

So montelukast, known under the prescription name of Singulair, is an oral leukotriene receptor antagonist. The proposed over-the-counter or OTC trade name is Singulair Allergy. Montelukast was approved in the United States for prescription use in 1998 for asthma, followed by prescription indications for exercise-induced bronchoconstriction, seasonal allergic rhinitis, and perennial allergic rhinitis.

Dosing is by age and is the same for all indications, except for the approved age range. So the 10 milligram tablet, which is what is proposed in this application for OTC use, is approved in the prescription setting for adults and adolescents, age 15 years and older.

Montelukast is also available as a 5-milligram chewable tablet for 6 to 14 year olds, a 4-milligram chewable tablet for 2 to 5 year olds, and as 4 milligrams of granules, which can be sprinkled on applesauce for ages 6 to 23 months.

The approved age range varies by indication, with seasonal allergic rhinitis approved down to age 2 years and perennial allergic rhinitis approved down to age 6 months.

So montelukast is proposed OTC for relief of allergy symptoms, which corresponds to the prescription indications for seasonal allergic rhinitis and perennial allergic rhinitis. Under the uses statement, Merck is also proposing to include itchy, watery eyes, which would be a new allergy indication for montelukast. The current prescription labeling does not include a claim for ocular symptoms.

Notably, the other prescription indications for asthma and exercise-induced bronchospasm are not proposed under this partial switch and would remain prescription. In addition, the proposed OTC indication is limited to adults with a do not use statement for children under 18 years of age. To address potential OTC use in asthma, Merck has proposed a highlighted warning at the top of the Drug Facts label, stating that this product is only

for allergies. Do not use to treat asthma.

The montelukast OTC development program relies on the safety and efficacy established for the prescription product since the allergic rhinitis indication is considered to be similar for both prescription and OTC use. As such, it's not necessary to reestablish efficacy for the OTC nasal allergy indication.

To support the new indication for ocular allergy symptoms, Merck submitted the results of three seasonal allergic rhinitis studies, which were previously reviewed as part of the Prescription Allergic Rhinitis program. The safety of montelukast is supported by the prescription safety database, which includes nearly 10,000 montelukast treated patients for all indications combined. The safety is also supported by extensive worldwide marketing from prescription approval in over 100 countries beginning in July 1997.

Based on this safety database, the prescription label contains warnings regarding

neuropsychiatric adverse events and eosinophilic conditions, including Churg-Strauss syndrome. Of these, neuropsychiatric adverse events are perhaps most pertinent to OTC use.

In order to address issues regarding potential OTC use in asthma and pediatric populations, as well as to assess understanding of the labeled warnings for neuropsychiatric adverse events, Merck conducted three consumer studies, which are outlined here in this table. These trials include a label comprehension study in adults focused on ages 15 to 17 years, which also included label interpretation questions regarding neuropsychiatric adverse events and a self-selection and label comprehension study in adult asthmatics, evaluating off-label use in asthma and in pediatrics.

To hear the presentations this morning, we ask you to keep the topics for discussion today in mind. These will focus on the benefit/risk profile of montelukast for over-the-counter treatment of allergy symptoms in adults. And as I noted

previously, we're not here to discuss the efficacy specifically related to OTC use of the nasal indication. However, given the newly proposed indication for ocular allergy symptoms, we've included this discussion question on efficacy, which will allow you to discuss both the ocular symptoms, as well as the benefit side of the benefit/risk profile of montelukast in the OTC setting.

We anticipate that the major discussion point for today will be safety, including both the clinical trial and postmarketing databases, as well as consumer studies. In your discussion, please include areas of potential concern, namely neuropsychiatric adverse events, OTC use for the treatment of asthma, and pediatric use. Neuropsychiatric adverse events of interest include agitation, aggression, suicidal thinking, and sleep disturbances.

The potential use by OTC consumers for the treatment of asthma is complicated by the considerable overlap between these two conditions.

Currently, there are no asthma controller products approved for OTC use given that asthma is a potentially life-threatening disease.

Given the specific pediatric prescription use of montelukast, we ask you to address whether potential OTC use in children under age 18 is of concern, and if a discordance in labeling with a prescription product could cause confusion for consumers.

There is a separate discussion for comments regarding the proposed Drug Facts label and consumer package insert. Since Merck proposes to address the potential safety issues just noted through labeling, we are particularly interested in your comments regarding these issues. And finally, we ask you to discuss the benefit/risk profile for OTC use of montelukast. Note that the voting question focuses on nasal symptoms in order not to confound the vote for the overall product with the newly proposed ocular indication.

Before I close, I just wanted to mention the legal framework that gives FDA the ability to hold

advisory committees to ask for scientific advice and recommendations from experts in the field. As I noted previously, FDA takes very seriously the advice of the committee, however, the commissioner does hold sole discretion on actions taken with regards to drug approval, especially since there may be other issues, such as manufacturing, that are not discussed at this meeting.

That's it for this morning. So I will turn the podium back to Dr. Parker. Thank you.

DR. PARKER: Thank you, Dr. Michele.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel

expenses, honoraria, and interest in the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with the sponsor's presentations.

Sponsor Presentation - Edwin Hemwall

DR. HEMWALL: Good morning. I'm Ed Hemwall from Merck Consumer Care, and we're here today to present our rationale and data supporting the switch of Singulair Allergy to over-the-counter status. I'm going to start repeating a few of the things that Dr. Michele outlined, so bear with me as I give these slides, which cover some of the same material, but I think it's important to reinforce.

The prescription Singulair, montelukast, was first approved in the U.S. in 1998 for the

treatment of asthma. And the first allergy indication for seasonal allergies was approved in 2002, followed by approval for perennial allergies in 2005, and prevention of exercise-induced bronchoconstriction followed in 2007. Montelukast is a leukotriene receptor antagonist and the only one of this class approved in the United State for allergic rhinitis. And it's been prescribed for allergies for about 12 years.

Singulair has an extensive history of clinical study and prescription use for all indications. It was evaluated in more than 100 clinical trials involving more than 20,000 patients receiving montelukast. It's been prescribed for the past 16 years and has been among the top ten prescribed medicines in the United States from 2005 to 2012. And this experience includes over 24 billion dose units distributed at an estimated 66 million patient-treatment years.

Prescription Singulair is approved at specific doses, dosage forms, and age ranges for pediatric use for the prophylaxis and treatment of

asthma in patients 12 months and older, acute prevention of exercise-induced bronchoconstriction in patients 6 years and older, and relief of allergic rhinitis in patients 6 months an older. It's taken once daily and is available in 4-, 5- and 10-milligram strengths, depending on age, with the lower doses supplied as a chewable tablet or granules for mixing with food.

The proposed OTC indication is for the temporary relief of symptoms due to hay fever or other upper respiratory allergies. The symptoms benefitting from treatment include nasal congestion, runny nose, itchy, watery eyes, sneezing, and itching of the nose. This indication is similar to other OTC allergy products and is supported by data in the approved prescription new drug application. As you know, we're asking for itchy, watery eyes to be included among the symptoms relieved in the OTC label, so the strength of the data supporting that ocular symptom claim will be discussed today.

The proposed OTC dose is 10 milligrams once

daily, the same as the adult prescription dose for allergy. But the recommended age is for adults 18 years of age and older. Thus, the proposal for Singulair is termed a partial switch because the asthma and pediatric indications would remain prescription status.

One consideration in any partial switch is the extent to which consumers might use the product for a prescription indication. And as you'll see, we have considered and studied this potential in depth and have developed effective labeling to manage this risk.

This is not an unusual situation. It's our many examples of OTC products, which have coexisting prescription indications for more serious conditions. Examples include proton pump inhibitors for frequent heartburn, and NSAIDs for analgesia. Nonetheless, unlike those prior examples, we've taken the additional precautionary step of creating prominent label warnings against any use to self-manage asthma.

Although allergy and asthma are distinct

disease states, they often coexist in the same person. Close to 8 percent of the U.S. population suffers from asthma, and up to 90 percent of them also have allergies. Many of them are using a range of OTC products to treat their allergy symptoms. And as we know from numerous sources, including studies conducted for this switch, consumer select products based on the symptoms treated, what it says on the package. And as you can see, the symptom complex here is very different. Allergy symptoms predominantly affect the nose and eyes, whereas asthma primarily involves the lungs and airways.

In the U.S., allergic rhinitis is the fifth most common chronic disease, affecting nearly 75 million Americans. Its prevalence extends to 20 percent or 1 in every 5 Americans. So it's no surprise that consumers rely on the availability of over-the-counter medicines to manage their allergy symptoms. This highly prevalent condition has a long history of self-care and consumers are accustomed to this well-established OTC category.

Ninety percent of people with allergies self-treat regularly or occasionally. Nearly 60 percent only use OTC medicines or herbal products for their symptoms. And allergy is not a trivial matter. Patients report that their symptoms have a substantial negative effect on their daily life. Forty percent say they have a moderate to severe impact and 38 percent report an even greater effect that they cannot tolerate the discomfort from their allergies. In fact, among those with moderate to severe symptoms, more than 90 percent report that their symptoms affect their ability to perform daily activities.

Eighty percent of those with allergies report difficulty sleeping and increased daytime fatigue. And allergies are also a major cause of work absenteeism, with nearly 10 million missed or lost workdays each year.

Despite being an established category, consumer responses to the current options vary, and many with allergies are not fully satisfied with the level of relief they obtain from their current

OTC choices. Seventy-five percent report they want more OTC allergy treatment options. And research shows that allergy treaters use an average of two or more different medications. In addition, 35 percent of OTC allergy product users report switching among products with different antihistamines or other combination ingredients, and they're looking for a regimen that helps them to best manage their symptoms.

The current allergic rhinitis treatment landscape features a range of products, and this chart lists the benefits and limitations of the major OTC categories as reflected in their OTC labeling. Across the top of the categories and within each column, I'll note their benefits with a check, and they're labeled "limitations" with an X.

First generation antihistamines are effective at relieving nasal and ocular symptoms, but they are known to cause drowsiness. Second generation antihistamines were developed to reduce or eliminate the drowsiness and offer the benefits of once daily dosing. However, some cannot be used

by certain consumers, such as elderly or those with liver or kidney disease without consulting a physician.

When a decongestant is added to an antihistamine, congestion relief is also provided. However, pseudoephedrine, the predominant ingredient in this category, may cause side effects, including insomnia or excitability, and has potential safety concerns in people with cardiovascular disease, diabetes, or glaucoma.

Cromolyn, a mast cell stabilizer, is also available for nasal symptom relief. And while effective, it requires frequent dosing and is an intranasal spray, which is not preferred by some consumers. An intranasal steroid spray is also not available OTC, and steroids offer nasal symptom and congestion relief with once daily dosing but do have label precautions or on use with other steroid products and in certain medical conditions. Clearly, every product works differently, and no one product is right for everyone.

This is what the landscape of options would

look like if Singulair Allergy were available as requested today. The introduction of a new choice, a leukotriene blocker, will offer distinct benefits to consumers, but with fewer of the limitations present in the category today. These additional benefits are provided by Singulair Allergy's unique and distinctive mechanism of action. It offers 24-hour relief of nasal and ocular symptoms, plus relief of nasal congestion is achieved without causing the adrenergic stimulation seen with OTC agents like pseudoephedrine or phenylephrine.

So Singulair can be used by people who might not be able to take those OTC decongestants due to conditions like hypertension or heart disease. And Singulair Allergy is also non-sedating and can be taken safely together with all other allergy medications.

When we think about an OTC switch potential, Singulair meets all of the key criteria that are often considered. This condition, allergic rhinitis, is readily self-identified and self-treated. It has a well understood safety

profile in controlled clinical trials and postmarketing use. It has no potential for abuse and is safe in overdose situations, being well tolerated at doses, which are many multiples of the 10-milligram therapeutic dose. No dose adjustment is needed for people with kidney or liver disease, and there are no clinically important drug-drug interactions. And it can be taken without regard to timing of meals.

A main focus of our presentation today will be on the OTC labeling for this product. Although OTC labeling for allergy is well established, Drug Facts labeling for Singulair Allergy requires some additional communication objectives.

One, it should not be used to self-manage asthma, and users should not change their asthma medicines; two, the OTC product is for adults 18 and over; and three, to make consumers aware of the potential for infrequent changes in behavior or sleep that have been reported during postmarketing surveillance. As you will hear, these adverse events associated with leukotriene blockers are

typically mild and reversible upon discontinuation. A causal relationship has not been established. However, we feel that it is important for consumers to have this information.

Our development program tested these key labeling elements in three studies involving over 1600 consumers, and the results you will see today demonstrated a high level of understanding with target populations scoring well in comprehension and self-selection studies. The main pivotal study was conducted entirely in asthma patients to specifically understand the choices they make when considering use of this product.

Here's an outline of the rest of our presentation. Drs. Stephane Bissonnette will review the key elements of the pharmacology, efficacy, and safety profile of Singulair. Then Ms. Arnita Arya will review the results of the three consumer behavior studies, providing the basis for our proposed Drug Facts label. And Dr. Stewart Stoloff, from the University of Nevada, School of Medicine, will provide a clinical

perspective on how OTC access for allergy might impact consumers with upper respiratory conditions, like allergy or asthma. And I'll return at the end to summarize our presentation.

In addition to other experts with us today from Merck, I would also like to call your attention to the panel of outside experts we have invited to join us in order to address any questions, which might benefit from their perspective. And all of these external experts have been compensated for their time and travel.

I'd now like to introduce Dr. Bissonnette, and thank you.

Sponsor Presentation - Stephane Bissonnette

DR. BISSONNETTE: Thank you, Dr. Hemwall.

Good morning, everyone. I am Stephane Bissonnette, director of the RX-to-OTC switch team at Merck Consumer Care. I would like to start my talk with a review of the pharmacology beyond the therapeutic effects of montelukast and leukotriene modifying agent in general.

Here's a schematic representation of the

early and late phase of the allergic response when the body is exposed to allergens. The key point in this picture is that in either phase, there are more mediators than the well known histamine that is released from mast cells. Over the years, several other mediators have been discovered in the inflammatory process associated with the upper respiratory allergies. Among these new mediators, leukotrienes are the only ones proven to be important based on the clinical efficacy demonstrated when the interaction with their receptors is prevented.

Leukotrienes are sensitized in both the early and late phases of the response to allergens and act to promote the inflammatory process leading to the well known nasal and non-nasal symptoms of allergic rhinitis. In fact, montelukast blocks the effect of these leukotrienes exerting its benefits in both phases, a unique mechanism of action compared to other current OTC treatment options.

Montelukast has a high affinity and selectivity for the cysteinyl leukotriene receptor

type 1 receptors. These receptors are found in the inflammatory cells of the upper airways, and when activated cause vascular permeability, edema, mucous production, and increase in eosinophil counts, which are all associated with the symptoms of up per respiratory allergies.

By blocking the leukotriene receptor, montelukast reduces these leukotriene-induced inflammatory effects and releases the major nasal and ocular allergy symptoms, including nasal congestion. This favorable impact on the inflammatory process represents an advantage over many existing allergy therapies, such as antihistamines.

Now, let's turn to the efficacy and safety established during the Merck development program for the prescription indications. As noted earlier, for all indication, for any dosage form, adult and pediatric, more than 100 clinical trials involving more than 20,000 montelukast-treated patients were conducted, providing a large clinical trial database.

Looking specifically to the allergic rhinitis indication, the efficacy and safety of Singulair were established in a program of 10 phase 2 and 3 clinical trials with similar design, where more than 3,000 montelukast-treated patients were involved. Eight of them were for seasonal allergic rhinitis, including five phase 3 trials, and the other two for perennial allergic rhinitis.

As shown here, a total of four trials were classified as pivotal, three in seasonal and one in perennial allergic rhinitis because these studies were prespecified as pivotal at the time of the original filing with the FDA for the Rx approval of allergic rhinitis. They all used the primary endpoint of Daytime Nasal Symptom Score to demonstrate the efficacy of montelukast.

Several endpoints were part of this development program, and they were the same for all studies, providing the opportunity to pool the data to account for variability. These endpoints included the key element of nasal and ocular symptoms. As part of the nasal symptoms, the most

bothersome symptom, nasal congestion, was measured during both daytime and nighttime.

As for ocular symptoms, the Daytime Eye Symptom Score was measured, which included itchy, watery eyes as the symptoms of tearing eyes and itchy eyes. To date, you're being asked to consider the data supporting the inclusion of itchy, watery eyes in the OTC label for Singulair Allergy. While nasal symptoms are listed in the prescription label, the ocular symptoms are itchy, watery eyes or not, despite consistent efficacy that was demonstrated throughout the development program. The reason for the absence on the Rx label is that they were part of the secondary endpoints, which were not corrected at that time for multiple comparisons using a prespecified analysis.

We are requesting itchy, watery eyes be included on the list of symptoms for the overall allergy medication, as it is important for consumers to be aware of the total potential benefits that a medication may have on their

allergic rhinitis. This request is supported by the original clinical trial data from the entire phase 2 and 3 development program.

Now, let me go through the data that support the addition of ocular symptoms relief. Here's the individual improvement in the eye symptom score of montelukast versus placebo from the five phase 3 trials that were conducted in seasonal allergic rhinitis. As you can see, four of them have reached statistically significant differences with a p-value less than .05.

As mentioned previously, Daytime Eye Symptom Score was one of the secondary endpoints. And if you applied the Bonferroni adjustment for multiple comparisons to the secondary endpoint post hoc, a p-value less than .01 reflects statistical significance. By applying this multiple comparison adjustment to all phase 3 SAR studies, the Daytime Eye Symptom Score is statistically significant in three of the five studies.

Now, looking specifically to the three pivotal SAR studies and their pooled analysis for

the ocular symptoms, as highlighted, montelukast improved the Daytime Eye Symptom Score versus placebo. The pooled analysis accounts for the variability among studies, which is not unexpected, based on the subjective nature of the assessments and the spontaneous variability in the disease. Also shown are the four individual eye symptoms that contribute to the overall score.

As you can see, the overall improvement is equally supported by all four individual symptoms, which showed significant improvement, including itchy and watery eyes. These results are further supported by an independent meta-analysis of six publications by Gane and Buckley, published in 2013, that demonstrated similar results that the overall mean change from baseline from the eye symptoms score was statistically significant versus placebo, as shown in the yellow box.

This slide shows the magnitude of the effect size of the difference between montelukast and placebo for the eye symptoms and nasal symptoms scores. The clinical relevance in the improvement

in the eye symptoms score is also supported by the fact that the effect size is comparable to that of the Daytime Nasal Symptom Score. This is important because the clinical efficacy, demonstrated on the Daytime Eye Symptom Score, was the basis for the approval of Singulair for allergic rhinitis. While the effect size for the eye symptoms score may appear modest, it still meets the same bar for which Singulair was approved for allergic rhinitis.

Of note, the baseline eye symptom score was 1.45 on a scale of zero to 3 compared to the baseline nasal score of 2.11. As you know, showing significant improvement from a lower baseline value is more difficult. Nevertheless, improvement in the eye symptoms score is of the same magnitude as the daytime nasal score.

Furthermore, the clinical relevance of the eye symptoms improvement is also shown by the improvement in the Juniper Rhinoconjunctivitis Quality of Life Questionnaire, a validated tool to assess by the patient the burden of their allergic rhinitis symptoms. This too was used throughout

the entire development program for Singulair for both seasonal and perennial allergic rhinitis.

Singulair has shown improvement, versus placebo, not only in the overall questionnaire but also in the specific eye symptom domain in three of the four pivotal allergic rhinitis studies, as highlighted here, where the confidence interval doesn't include zero.

In summary, taking all the available evidence together -- the clinical relevance and addition of itchy, watery eyes -- to the OTC label is supported by:

1) the result of each study as well as the pooled analysis of the pivotal trials showed that montelukast improved the eye symptoms score versus placebo;

2) the individual symptoms of itchy eyes and watery eyes in the pivotal trial analysis also show improvement;

3) the effect size of the Daytime Eye Symptom Score is in the same magnitude as the Daytime Nasal Symptom Score, which was the basis

for the Rx approval of Singulair for allergic rhinitis.

Finally, when looking at the burden of symptoms, as assessed by the Validated Patient Quality of Life Questionnaire, Singulair has shown improvement versus placebo not only for the overall questionnaire but in the specific eye symptoms domain in both seasonal and perennial allergic rhinitis. Thus, the totality of the evidence provides clinical relevance that shows that montelukast is effective for the relief of itchy, watery eyes and provides support for the addition of these symptoms to our OTC label.

Now, let's turn our attention to the safety profile of montelukast. This safety profile is well established in more than 100 clinical trials in asthma, in exercise-induced bronchoconstriction, in seasonal and perennial allergic rhinitis, in both the pediatric and adult populations.

The clinical development program, for all its different indications, montelukast 10 milligrams exhibited an adverse event profile

comparable to placebo. Furthermore, there were no drug-related, serious adverse events in any allergic rhinitis studies during the development program for Singulair. As a reminder, ten of these trials were for allergic rhinitis, including more than 3,000 montelukast-treated patients.

This table shows montelukast adverse events that occurred in 1 percent or more patients and at a frequency greater than placebo in the allergic rhinitis development program. The comparison shows that the overall rates were quite low and similar between montelukast and placebo groups in both the seasonal and perennial allergic rhinitis studies. The most frequently reported adverse event in these studies was upper respiratory infection.

So this safety profile observed in the allergic rhinitis development program is not only favorable in the Rx setting but also is what we would want for any product in the OTC environment. The safety profile of montelukast has also been assessed at doses as high as 90 times the recommended 10-milligram tablets for adults.

In chronic studies, montelukast was given at dosage as high as 200 milligrams per day for 22 weeks. And in short-term studies, up to 900 milligrams per day for approximately one week. No new clinically important adverse events were observed in these trials. The adverse events were consistent with the safety profile of the regular 10-milligram tablet of Singulair. This highlights the large safety associated with this medication, which is an important feature for a product in the OTC environment.

In terms of postmarketing experience, Singulair has more than 16 years of use in the market for both adults and children in more than 100 countries. It has been among the top ten prescribed medicine in the United States since 2005. Twenty-four billion dose units have been distributed since its market introduction, reflecting an estimated 66 million patient-years of exposure.

While Singulair postmarketing safety profile has been generally consistent with the profile

found during the clinical development program, their prescription label has been updated in several sections over time to reflect new information obtained from new clinical trials and from adverse event reported from the real-world use. This process is not unique to Singulair, and it is part of the typical evolution of any product label.

Listed here are the ten most frequently reported adverse events, regardless of causality, found in our internal safety database for Singulair since market introduction through 2013. Given the high usage of montelukast for asthma and allergic rhinitis, it is expected that a variety of spontaneous report with different adverse events are captured in our internal safety database. Events such as headache, rash, and abdominal pain were also reported in our clinical trial experience.

Reports regarding nervous system and psychiatric events were received during marketed use, and terms associated with these events have

been added to the Rx label over time. Merck along with the FDA has carefully evaluated the neuropsychiatric events including some rare events related to suicide and suicidal behavior. They have also examined similar data from both the clinical trials and postmarketing experience from the other two main factors of leukotriene modifying agents.

FDA posted on their website the result of their evaluation in early 2009. They concluded that the clinical trial data do not suggest that leukotriene modifying agents are associated with suicide or suicidal behavior with the caveat that the studies were not designed to examine these events.

They also mentioned that the clinical details of some postmarketing reports of neuropsychiatric or behavior-related events are consisted with a drug-induced effect. Later in 2009, the FDA requested that the manufacturers of leukotriene modifying agents add a precaution on their prescription label and that healthcare

professionals and patients be aware of the potential for these events. The OTC labeling will provide similar information as the Rx label aimed at consumers in both the Drug Facts label and in a consumer information leaflet provided as a package insert.

As you will see in a moment, our research indicates that the language related to these label warnings tested well with consumers and will support the safe use of Singulair Allergy in the OTC environment. To summarize, the safety profile from the clinical trial demonstrates that Singulair has an adverse event profile comparable to placebo.

A Merck review of the neuropsychiatric event, that was shared with the FDA, shows that suicidality was quite rare and behavior-related adverse events infrequent. In 2009, FDA came to a similar conclusion in their own analyses from the pooled clinical trial data of all three manufacturers of leukotriene modifying agents. Based on the postmarketing experience, the Rx Singulair label has been modified over time to

reflect the most current information, which has been incorporated in the OTC label to support the safe use in an OTC environment.

In closing, montelukast is an effective and well-tolerated, once daily overall therapy with the mechanism of action different from any other agent approved for the treatment of allergic rhinitis and, thus, will be an important addition to the current therapeutic options for allergic rhinitis.

Now I would like to turn the podium over to Ms. Arya, who will review the studies which support the label development for Singulair Allergy. I would like to thank everyone for your attention this morning. Thank you very much.

Sponsor Presentation - Arnita Arya

MS. ARYA: Thank you, Dr. Bissonnette.

Good morning. I'm Arnita Arya, and I'm responsible for consumer research relating to Rx-to-OTC switches at Merck Consumer Care. My goal this morning is to take you through the objectives of our OTC development program, the iterative process that we employed to develop an effective

Drug Facts label and the results of consumer studies, which demonstrate that these objectives were successfully achieved.

As you have seen this morning, the safety and efficacy of Singulair were established with the initial approval of the prescription product. Therefore, the ultimate goal for a switch program is to develop a Drug Facts label that guides appropriate self-selection and is well understood. It should contain relevant warnings so that consumers can safely use the product in an OTC setting.

The studies I would like to take you through now demonstrate that consumers clearly understand all aspects of the Singulair Allergy label and can appropriately self-select to use this product to treat their allergy symptoms and not to treat asthma. We designed our consumer studies to address issues raised by the FDA to ensure appropriate use and to prevent potential off-label use.

As a result, we had three program goals.

First, our pivotal study, SOLID, was executed to assess if asthma sufferers understand that Singulair Allergy should not be used to treat their asthma. SOLID was a combined self-selection and label comprehension trial with 820 adult asthma sufferers.

Next, to assess if the behavior-related label warnings were well understood, we conducted a targeted label comprehension study, focusing on these specific warnings among 480 adult allergy sufferers.

Finally, we conducted a self-selection study among 350 teens, 15 to 17 years old, to see if teens understand that Singulair Allergy is only intended for adults. In addition to assessing self-selection among teens, we also looked at their interpretation of the behavior-related warnings to see if they would understand this portion of the label in the event they used this product off label.

Before I share the details of the consumer studies, let me take you through the proposed

Singulair Allergy Drug Facts label. As you can see, the product is clearly labeled for the treatment of allergies. Likewise, the label clearly states that the OTC product should not be used to treat asthma. Also, it includes the appropriate behavior-related warnings in concise, consumer-friendly language. Finally, the product is clearly labeled to be used by adults only.

Now, I will take you through the key study results starting with SOLID. SOLID focused on asthma sufferers with and without allergies. SOLID was a robust single-visit study that took place at 17 market research and clinical research facilities across the U.S. It followed FDA guidance for studies of this type. Minority populations and consumers with low literacy were well represented. All thresholds and mitigations were defined a priori.

We enrolled 733 adult general population asthma patients in the SOLID study; 592 had asthma with comorbid allergies and 141 reported having asthma only. This distribution is consistent with

the overall U.S. asthma population, where up to 90 percent of asthma sufferers have concomitant allergic rhinitis.

It was believed that consumers who were familiar with prescription Singulair could potentially be more likely to use Singulair Allergy off label in an OTC setting, so we assessed this potential for off-label use among asthma sufferers by including both subjects with prior experience using prescription Singulair and those who had never used prescription Singulair.

349 subjects had no prior experience using prescription Singulair and 384 did have prior experience with prescription Singulair. A priori thresholds were set for these two groups. In addition, 163 subjects with low literacy skills were also studied. Seventy-six subjects came from the general population of 733 adult asthma patients and 87 additional asthma patients with low literacy skills were enrolled.

SOLID's primary endpoint was self-selection. The target threshold for the primary endpoint was

set as a lower bound of the 95 percent confidence interval being greater than a 90 percent target for each cohort, those with prior experience with prescription Singulair and those with without.

A correct self-selection decision was based on the subjects stating that they believed the product was appropriate for them to use to relieve their allergies or allergy symptoms and not to treat asthma. Subjects were handed the OTC Singulair Allergy package and given the opportunity to review at their own pace. Then they were asked the self-selection question, is this product appropriate for you personally to use or not? A series of open-ended follow-up questions were then asked to assess the rationale for their selection decision to determine if their decision was correct or incorrect; specifically, what, if anything, would you personally use this product to treat?

This question was asked to clarify if they intended to use the product for their allergy symptoms or for asthma. Two standard follow-up questions were also asked to understand the

rationale for their self-selection decision.

Now, let me take you through the results of the SOLID study. SOLID self-selection results were strong regardless of whether consumers had prior experience with prescription Singulair or not. Among the adult asthma sufferers with no prior experience using Singulair, the primary endpoint was met. Ninety-six percent made a correct self-selection decision. Among adult asthma sufferers with prior experience with Singulair, 92 percent made a correct self-selection decision. The lower bound was 88 percent and nearly met our a priori threshold.

Now, evaluating asthma-only subjects at the self-selection question, is this product appropriate for you to use and why, showed that 50.3 percent appropriately selected not to use this product, but the remainder, 49.7 percent initially seemed to be potentially incorrect. However, when the potentially incorrect selectors were asked the follow-up question, what they would use this product to treat and why, it became clear from

their responses that an additional 40.4 percent would use the product to treat their allergies or allergy symptoms and not asthma.

This shows that subjects who self-reported suffering only from asthma and not allergies achieved 90.8 percent correct self-selection, which is similar to the self-selection results among prior Singulair users and non-users.

A sample of verbatim responses from the self-reported asthma-only subjects shown here demonstrate the point. When asked why did you say that, the responses pointed to appropriate use of this product. They said things like, "Because it's an allergy medicine. And if I had allergies, I could use it." "Because my eyes bother me a lot." "To relieve runny nose and sneezing." Thus, it is clear that some asthma-only subjects who selected Singulair Allergy would only use it to treat their allergy symptoms or allergies and not asthma.

Now I'll discuss the secondary endpoints in the SOLID study. Secondary endpoints for the SOLID study were of specific communication objectives

relating to asthma on the Singulair Allergy Drug Facts label. They are, "Do not use to treat asthma." "Do not stop taking current asthma medicines when using Singulair Allergy." "Do not use under the age of 18."

The target threshold for the secondary endpoint was set as a lower bound of the 95 percent target being greater than the 90 percent target. I'll now take you through these results.

The two sections of the label communicate that consumers should not use this product to treat their asthma. It is highlighted in yellow, and it is repeated under the warning section with additional communication stating that asthma can be a life-threatening condition and you should follow your doctor's directions.

These two warnings together were effective in that 92 percent of asthma patients understood not to use Singulair Allergy to treat their asthma regardless of prior experience with the product. Ninety-five out of every 100 subjects clearly understood that if you are currently taking asthma

medications, you should not stop taking them when using Singulair Allergy. Specifically, 94 percent of asthma sufferers who had prior use of Singulair and 96 percent with no prior experience understood this warning.

Why is this important? First, it demonstrates strong comprehension to continue using the asthma medications, which require a prescription from a healthcare professional and also suggests that doctor-patient relationships remains intact. Also, subjects clearly understood that Singulair Allergy is for adults 18 and over. At least 96 percent of asthma sufferers understood this warning.

Importantly, when asked about their asthma management behaviors in the event of an acute attack, almost all asthma sufferers reported understanding what appropriate actions to take such as using a nebulizer or an inhaler, calling a doctor, or going to an emergency room. In addition, 93 percent understood to continue seeing their doctor for asthma when using Singulair

Allergy to treat their allergies.

In summary, SOLID successfully accomplished our first program goal of demonstrating that consumers clearly understand that Singulair Allergy is not to be used to treat asthma. The self-selection results were strong regardless of whether consumers suffered from allergies as a comorbidity, which most did. Also, self-selection results were strong whether or not consumers had prior experience with using prescription Singulair.

In addition, the key asthma warnings and other messages on the label were well understood. Subjects reported understanding of what to do in the case of a flare up, and that they should continue to see their physician for their asthma.

Now, let's turn to our remaining two studies. The next study in our OTC development program was a targeted label comprehension study to evaluate the effectiveness of the behavior-related warnings on the Singulair Drug Facts label and was conducted among adult allergy sufferers.

Before I review the results of the study,

let me provide some perspective relative to these warnings. As stated earlier in this presentation, postmarketing experience with Singulair has led to modification of the prescription label over time to include behavior-related warnings. Our objective for the OTC product was to design labeling to communicate these warnings on the Drug Facts label while also including a consumer information leaflet, which replicates the warnings listed on the current prescription patient insert.

Since Drug Facts labels typically do not list all adverse events from the prescription label, we developed a series of six potential warning statements that embodied the warnings on the prescription consumer insert. These six warning statements were tested with consumers to assess which options best captured the spectrum of potential behavior-related adverse events.

These in-depth qualitative and iterative tests showed that the two warnings on this slide accomplished this objective effectively. These are stop use and ask a doctor if you experience

unexpected changes in behavior, thoughts, or mood, and stop use and ask a doctor if you experience unexpected changes or problems when you sleep.

Now, let me take you through the methodology for the adult label comprehension warning study. This study recruited 480 adult allergy sufferers; 361 were general population subjects, while 151 had low literacy skills. Subjects were provided with the Singulair Allergy box and were asked a series of scenario-based comprehension questions related to the behavior-related warnings along with other masking questions.

The primary study endpoint was set as a lower bound of the 95 percent confidence interval being greater than a 90 percent target to assess comprehension of these warnings among a general population of adult allergy sufferers.

The primary endpoint was met. Adult allergy sufferers understood both the warnings. Ninety-eight percent understood the warning about unexpected changes in behavior, thoughts, or mood, and 97 percent understood the warning about

unexpected changes or problems with sleep.

We also examined the results in the subjects who have low literacy skills across both of the adult studies, and their scores ranged between 79 percent to 91 percent. This subpopulation on average scores 10 to 12 points lower than the general population, and these results are in line or better than expectations.

The last study for our final program goal was a teen self-selection and warnings interpretation study. It was conducted to confirm that teen allergy sufferers understand the proposed product is not for them. This study was designed with a step-wise approach. The first part was self-selection among teen allergy sufferers, ages 15 to 17. It was conducted given the prescription dosing for the 10-milligram tablet includes adolescents 15 or over, while the proposed OTC product is indicated only for adults 18 and older.

Teens were asked a self-selection question, is this medicine okay for you to use, and then asked follow-up questions to obtain the rationale

for their selection decision. Furthermore, if they did say they would use this product, an additional question was asked to determine if they would take this product on their own or would ask someone first.

The second part of the study focused on teens' understanding of the label warnings in the event they would use this product against the age directive on the label. They were asked an open-ended question, if you were taking this medicine and started feeling different than you usually do, what, if anything, would you do? Their responses were evaluated to determine if they reflected a safe intended action.

In this study, we define safe intended action as a response in which the teen would communicate a potential drug-related effect to a parent, family member, doctor, or pharmacist, or would stop using the drug. Teens were asked to explain in their own words what each label warning meant. There is no FDA guidance for interpreting teen self-selection and label comprehension

results, so we simply chose to use the adult thresholds for teens.

The study results showed that 84 percent of teens with allergies appropriately self-selected not to use this product based on the label age directive. Ninety-seven percent of all teens indicated that they would communicate a potential drug-related effect to a parent, family member, doctor, or pharmacist, or stop using the drug in the face of a potential adverse event.

Further, teens were able to tell us in their own words the meaning of the two behavior-related warnings on the Drug Facts label. Ninety-five percent of teens understood the warning concerning changes in thoughts, behaviors, and mode, and 96 percent understood the warning concerning changes in sleep. It's important to note that these comprehension scores are comparable to what was observed among adult allergy sufferers.

We recognize that the self-selection scores among teens were lower than the general population, so we looked into the responses of the incorrect

self-selectors. Fifty-two of the 55 teens who inappropriately selected to use the product responded with a safe intended action in the face of a potential adverse event, and 52 to 53 understood the behavior-related warnings.

In summary, these three consumer studies demonstrate that Singulair Allergy Drug Facts label is well understood and provides consumers with the information necessary for safe and appropriate use in the OTC environment. First, consumer behavior studies show high comprehension that Singulair Allergy is not intended to treat asthma. Second, the behavior-related warnings are well understood by both adults and teens. And third, teens understand Singulair Allergy is not intended for them.

Now I would like to ask Dr. Stoloff to offer a clinician's viewpoint on the impact of Singulair Allergy being over the counter.

DR. PLATT-MILLS: Dr. Parker, can I ask a simple question about the labeling?

DR. PARKER: I think if you can just hold

it, we're going to let them finish, but we'll come right to you.

DR. PLATT-MILLS: It really matters --

DR. PARKER: We want you to use the mic.

DR. PLATT-MILLS: It's about the issue of time of day. I don't see anything here in the labeling.

DR. PARKER: So we'll put that at the top of our order in clarification and just note it, so we can let them go through it. Thanks.

Sponsor Presentation - Stewart Stoloff

DR. STOLOFF: Thank you, Ms. Arya.

My name is Stewart Stoloff. I'm a clinical professor of family and community medicine at the University of Nevada School of Medicine, Reno. I also am a member of the NIH National Heart, Lung and Blood Institute's expert medical panel, Guidelines for the Diagnosis and Management of Asthma. In addition, I've been a member of the Task Force on Allergic Disorders of the American Academy of Allergy, Asthma, and Immunology.

I thank you for your time this morning to

talk about the clinical considerations raised by the potential nonprescription switch of Singulair Allergy. I'd like to start my talk by placing allergic rhinitis into context. It is not simply a runny nose. It is a global health problem that affects hundreds of millions of people from all countries and of all ethnicities and ages.

Data show that it has a major effect on patients' lives, interfering with sleep, social life, school, work, attendance, and productivity. In fact, in the U.S. alone, allergic rhinitis accounts for an estimated 28 million days of restrictive activity or reduced productivity on an annual basis. This is not surprising seeing as about half of patients with allergic rhinitis experience symptoms for more than four months out of the year, and 20 percent of have symptoms for at least nine months out of the year. It is not insignificant, and from a health perspective causes major illness and disability worldwide. Allergic rhinitis is a condition that deserves attention.

Since 2007, the allergic rhinitis in its

impact on the asthma expert panel, also known as ARIA, has developed statements, position papers, and recommendations for allergic rhinitis worldwide. The latest treatment algorithm on allergy management was published in 2012. It recommends intranasal corticosteroids as first-line agents. But it is important to point out that the benefits of leukotriene antagonists in allergic rhinitis are also well recognized by world experts.

These agents have a role as valuable alternatives and effective treatments from mild to moderate and even severe allergic rhinitis. Moreover, the ARIA expert panel acknowledges that patients overwhelmingly treat their allergies with OTC medications.

As you've heard today, as many as 90 percent of patients with asthma also have allergic rhinitis. However, the symptoms are quite different and obvious. Allergic rhinitis affects the upper airway, the nose and eyes, causing nasal itching, sneezing, congestion, as well as eye itching, tearing and redness after exposure to

certain triggers.

Conversely, asthma affects the lower airway, the chest, and is predominantly characterized by wheezing, chest tightness, -shortness of breath, most often occurring in cold air with exertion or at night. Asthma patients recognize the difference between their asthma and their allergic rhinitis. Let me tell you, there is nothing more unsettling to anyone than the inability to breathe.

As we all know, asthma is a chronic life-threatening condition. So what might be the risk to this population if they were to choose OTC montelukast? From a clinician's point of view, there is minimal risk. Let me be clear. I am not advocating off-label use, but there could be a benefit.

Multiple studies have identified that the addition of montelukast to another controller medication can result in improvement in both day- and nighttime symptoms, quality of life, lung function, as well as reducing the risk of asthma exacerbations as defined by emergency room visit,

hospitalization, or need for oral corticosteroids; nor is there an indication that OTC availability of Singulair will negatively impact how patients with asthma interact with their healthcare providers.

This is a patient population that relies on prescription medications. Every patient with asthma requires, at minimum, a prescription quick-relief inhaler, a rescue medication. The majority, up to 60 percent, take at least two medicines. And we know that roughly 85 percent of patients with asthma report they do see their primary care physicians at least twice a year.

Based on these statistics, as well as my own clinical experience, and in observing how patients with other chronic diseases interact with their physicians, there is no reason to believe that asthma patients will sever their relationship with their healthcare providers. Further, it is extremely unlikely that patients will substitute OTC montelukast for their rescue medication.

Findings from the 2009 Asthma Insight and Management Survey demonstrate that 81 percent of

asthma patients reported using a prescription quick-relief medicine at some point, and more than half of these patients had used one within the past month.

Montelukast is only available in pill form and not as an inhaler. There is no culture of use of oral medications to treat acute exacerbations. To the contrary, there's a long history of the use of rescue inhalers for rapid relief of acute symptoms. So while the absolute risk cannot be unequivocally ruled out, it is highly unlikely that patients with asthma will confuse this product for their rescue medications. I don't believe that patients with asthma will be at greater risk with the availability of Singulair Allergy.

But the other question remains. Why do we need another OTC option for allergy? Allergic rhinitis is distinct and unique in each patient, and so having various treatment options is common sense. Despite options presently available, allergic rhinitis remains a burden and is not a well-controlled disease for many sufferers.

Having another medication with a unique mechanism of action is not only appropriate, it is needed. Broad clinical experience indicates, and my own experience confirms, that patients are not always comfortable using nasal corticosteroids often due to side effects or delivery method. Other current options may not relieve their particular constellation of symptoms. For many of these cases, physicians prescribe Singulair. It resolves allergies and relieves nasal and eye symptoms. And from an adherence standpoint, a once daily tablet is simply a better option for many patients with allergic rhinitis.

As clinicians, our goal is to work with our patients to improve their quality of life. They want options. Singulair Allergy represents another treatment option for our patients. Off-label use to treat asthma is unlikely to occur. And in those rare circumstances where it does, adverse outcomes, including severing doctor-patient relationships are very unlikely. The benefits of OTC availability for allergy substantially outweigh any risk beyond

those that currently exist. For these reasons, an additional treatment option makes sense.

Thank you for your time and attention.

Sponsor Presentation – Edwin Hemwall

DR. HEMWALL: Thank you, Dr. Stoloff.

As discussed earlier, Singulair has a novel mechanism of action that can benefit consumers with allergies who want a new treatment option or who may not be able to use certain products due to comorbidities such as diabetes, cardiovascular disease, or glaucoma. And Singulair also has a well established safety profile, no drug-drug or drug-food interactions, and it can be used safely with other allergy products.

Singulair is the only single-ingredient tablet available to treat all major allergy symptoms, including nasal congestion and ocular symptoms. It is important that the label accurately reflects the full range of symptoms relieved so that consumers can make an informed decision and avoid unnecessary use of additional products.

Let's return to the chart that I presented at the start of our presentation. We know that every product currently available for OTC treatment of allergy works differently, and no one product, including Singulair Allergy, is right for everyone. But Singulair does provide distinct benefits without some of the limitations present in the category today. And the reason this profile of benefits and limitations shown here looks different is because Singulair is different.

You've seen the results from our OTC development program. They demonstrate that the product can be used appropriately in an OTC setting. Given the overall prevalence of allergy, greater availability of a unique product like Singulair would offer an important new choice for U.S. allergy sufferers, especially for those who may not be able to take current OTC decongestants.

However, as with all OTC medications, we must consider potential incremental risks of OTC access compared to what risks already exist with prescription use. And those concerns have been

carefully considered and addressed with our proposed Drug Facts carton labeling, which has been tested according to methods published in FDA guidelines.

We're also proposing to provide a consumer information leaflet, a package insert, which contains additional information lifted directly from the patient information leaflet, which is currently available with prescription Singulair. The Drug Facts label and even the product name were developed to clearly communicate that this product is only for allergy. This labeling is well understood and provides consumers with the information needed for safe and appropriate use.

Consumer behavior studies demonstrated high comprehension that the product is not to be used to self-manage asthma, and the behavior-related warnings as well, understood by both adults and teens. And teens understand the product is not intended for them. And if they were to use it anyway, it's safe for them to do so.

In conclusion, montelukast has been a

mainstay of prescription allergy therapy for years. Singulair Allergy meets the criteria for an Rx OTC switch for allergic rhinitis and readily fits into the traditional OTC paradigm. We appreciate the committee's interest in our presentation today, and we are ready to respond to your questions. Thank you.

Clarifying Questions

DR. PARKER: Well, we either get a longer time for questions, longer time for a break, or maybe both. But I know I am seeing some eyes moving our way, so let me ask that for clarifying questions -- Dr. Platts-Mill, yes, you are going to get to go first, but hang on just a minute.

(Laughter.)

DR. PARKER: I'm going to ask those who have questions to make sure that they make Ms. Bhatt, to my right here, aware that they'd like to be put in the queue and get a head nod from her so that you are on the list. And certainly we do want to have time for clarifying questions, so we'll move right ahead. And Dr. Platts-Mill, you get to go first.

I will ask that you be sure to state your name clearly. And if possible, make your question as clear as possible and directed, if you're able to, to a specific speaker. So, Dr. Platts-Mill, let's go.

DR. PLATTS-MILL: This is Tom Platts-Mill. Is there anything in the labeling that says what time of day the tablet should be taken? And if not, why was that -- is there a basis for that decision?

DR. HEMWALL: That's a good question, and the answer is no. There's nothing in the labeling regarding time of day, and it's not in the prescription labeling either. The studies that were done to show efficacy did not specify a particular time of the day. The efficacy works if it's taken -- it works if it's taken once daily.

DR. PLATTS-MILL: Do you mean that Singulair never had indications that it should be taken in the evening when it was originally marketed?

DR. HEMWALL: Not that I'm aware of. Dr. Philip may have some additional history. He

worked on the original program

DR. PHILIP: George Philip.

DR. PLATTS-MILL: The package insert actually says once daily in the evenings.

DR. PHILIP: [Inaudible - off mic.] You are correct.

George Philip, Merck Research Laboratories. You are correct that at the time of its original approval for asthma, all of these clinical studies for Singulair were performed with evening dosing, and the labeling reflected that. For allergic rhinitis, however, as we moved forward into additional studies, the initial studies of Singulair for the new indication of allergic rhinitis were performed at evening dosing.

However, we did also perform a study explicitly with morning dosing in order to confirm that efficacy was demonstrated for allergic rhinitis with morning dosing. It's for that reason -- in other words, because efficacy was demonstrated both with evening dosing and with morning doses for allergic rhinitis, that the

labeling specific to allergic rhinitis is without regard to time of day.

DR. PLATTS-MILL: Sorry. Directly following that, were there instructions about the relationship to eating? Because that was a major issue in the early marketing of Singulair.

DR. PHILIP: So in fact, we have demonstrated with clinical pharmacology studies no significant food interactions. And all of the clinical trials, both in the original asthma development program as well as in the allergic rhinitis program, were performed instructing the patients to take the tablet without regard to timing of meals. So the available efficacy and safe data we have were whenever the patient took it in relation to whenever they ate the meal.

DR. PLATTS-MILL: Thank you.

DR. PARKER: Dr. D'Agostino?

DR. D'AGOSTINO: Ralph D'Agostino asking the questions. I have a couple of questions. One is that with the itchy, watery eyes -- is somebody crying?

(Laughter.)

DR. D'AGOSTINO: With the itchy, watery eyes and the Bonferroni correction, it's a very dangerous route to take in terms of doing that. Within each study, you had more than one variable that you looked at. So the alpha levels within each study should be inflated. And you can't carry away, say, a .01 from a particular study and bring it into this sort of meta-analysis that you're doing.

So I think as a committee -- as a statistician of the committee -- I do have to warn that we can't take away from that Bonferroni type analysis that the 3 out of 5 studies on page 14, slide 27 -- we really can't take away that that's an established fact.

Again, within each study, you've looked at more variables so that p-values within each study have to be inflated, have to be taken into account with the multiple variables you looked at. And then across the studies, you can do the dividing by .05, but it's all post hoc. So there's a lot of

issues that a purist would have and myself would have with carrying that into a conclusion. That's number one.

Number two is the other question. When you were looking at slide C-60, then you went to slide C-61, in 61, you took individuals' responses and you manipulated them to come up with a correct self-selection. Are the results that we're seeing in slide 60, have these undergone manipulation where you interpreted; they made a mistake, you interpreted until you found them saying the right thing?

I'm being facetious in saying that, but there seems to be some sort of interpretation of the results that you certainly have in slide 51 -- I'm sorry, not 61 -- and I'm wondering how much that is seen in your results in slide C-50.

Then also, in my last question is, in the 80 percent, 90 percent lower confidence bounds, I know you said that's what everybody does, but that's kind of large. I mean, the teens, 1 out of

5, could be making a mistake if it's a lower bound of 80 percent.

So I'd like to -- if you could give me quick responses to the issues I just raised, the Bonferroni, the manipulation to get what is meant by correct self-selection, and the interpretation of the lower bounds of these confidence intervals. Thank you.

DR. HEMWALL: There are a number of questions in there, and I want to have the statistical questions, Bonferroni, and why we look at the lower bounds of the confidence intervals in an observational study, not a hypothesis testing study. And I'll ask Dr. Larry Gould to briefly respond to those questions because we could get into a pretty good discussion, I imagine, with Dr. D'Agostino.

DR. GOULD: Larry Gould from Merck Research Laboratories; very good questions. Let me just tackle the Bonferroni one first. Now, this is a very thorny issue.

So the question would be, I guess if I had

to articulate how one might interpret this, in the studies -- there are three things that need to be established in terms of looking at the five studies. And again, understood that this is a secondary analysis. it's done after the fact. The first thing is to establish whether, in fact, taking all of the information together, one has substantial evidence that the product works.

Now, keep in mind, we are talking for the purposes of looking at ocular symptoms initially for the Total Ocular Symptom score. There were a number of secondary items, but that's -- in the sense that one could not demonstrate a significant treatment effect with the overall ocular symptom score, there would be no point to going forward -- and we wouldn't, of course, had gone forward -- with evaluating the individual symptoms such as itching, watery eyes and so forth.

So the first issue was did one establish, on the basis of the Total Ocular Symptom score across the studies -- across whether you've looked at all five or whether you looked at just the three -- the

answer to that question is yes, even if you use a Bonferroni correction, taken together. That's the first issue.

The second issue is the one where it is necessary to demonstrate substantial effect in at least two studies. That's part of the regulations if I understand them correctly. If that be the case, if you look at the five studies, then that also is true because you would then say by having established essentially a gatekeeper position with the overall global, then I could look at the comparisons for individual trials.

There are five individual trials. Three of them were significant at much less than .1 level. So the answer there would be, yes, one has established that the effect is real in at least two adequate and well-controlled trials.

DR. D'AGOSTINO: But aren't you -- I mean, we don't have in front of us what was done -- number one, with what was the intention of the protocol and the statistical analysis plan to look at this, and then an adjustment for the alpha

value with the error rate within each study.

So you're saying these results are so robust that if we made those adjustments, they'd still hold up?

DR. GOULD: Yes. Well, you do have the results. Let's back up a little bit. The issue is not nasal symptom score. The issue is -- and agreed, and admittedly, after the fact -- looking at the ocular symptom score. So let's take that and agree that this is not at the level where one ordinarily would do it for a typical NDA or a phase 3 confirmatory trial. But let's see. The point here, I guess, is to figure out what the evidence actually shows you.

Now, of the --

DR. D'AGOSTINO: I guess where I'm heading isn't so much that. It's that there are a lot of leaps that have to be made, with not planned, post hoc. So there's some comfort in looking at the numbers, but there's a lot of potential problems. Not potential. There are problems with doing something like this.

Just to make sure that the committee -- I want to make sure the committee understands that this is not the same as saying I went to five studies. I have one variable to look at. I've made a Bonferroni adjustment, and here's my results. I think -- not contradict in any of that.

DR. GOULD: Well, you're certainly correct about this being a post hoc evaluation, and it is based on a secondary evaluation. That part is true. And it is not up to the standard, as I said before, that one would ordinarily do with a pre-planned analysis. And we should perhaps treat this as an observation trial.

That said, however, the question is how might one understand the evidence, whether in fact it meets the usual standard for significance and adherence to the usual rules that one would associate with multiple comparisons. No argument there. I'd probably make the same points you did if I were in your position.

But again, that said, the question is, okay, understanding the limitations and understanding the

fact that this is not up to the usual standard, what interpretation might one reasonably make out of this information? And it seems to me -- again, it's my personal opinion. It does seem to me that the interpretation that one might make here is that one has, in fact, established that particular point in the sequence.

In other words, if one had not demonstrated an effect with all of the studies taken together on global ocular outcomes, that would have been the end of the story. That having been said overall, the question is, is it reasonable to believe that at least two of the studies had demonstrated the effect? Again, conceding the limitations, I believe it would be reasonable to believe that one could, in fact, accept that point.

DR. PARKER: Excuse me, because I think most of us can't do Bonferroni statistical analysis, but I think it's incredibly important. So in the interest of making sure we hear the other questions for clarification, what I'd like to ask is to make sure we capture the essence of the question that

came from our committee to you. And if you want to provide us more specific information about, as I understand it, the assumptions that were made statistically to come up with the finding that was presented, I think that might lend some clarity rather than just the opinion.

There were two other, as I understand it, specific statistical questions. So if I could ask you just to move on to those --

DR. GOULD: Sure.

DR. PARKER: -- so that we can go on to the other questions from the panel. There were two more I believe. Thank you.

DR. D'AGOSTINO: I'm just trying to eat up the time.

(Laughter.)

DR. PARKER: I'm trying to learn.

DR. GOULD: Okay. The instructing on the technical details obviously would be beyond what the bounds of the committee --

DR. PARKER: Yes. Let's go to the other two questions.

DR. GOULD: The questions, if I understand it correctly, had to do with how one interpreted the outcomes of the people who gave the "incorrect" answers of the question. So that's sort of like a broken up pie chart picture. So if we could put that up. I'm not sure which slide that is.

DR. PARKER: That's slide 51 --

DR. GOULD: Fifty-one?

DR. PARKER: -- with some interesting pie charts, as I recall.

DR. GOULD: Right. So the issue here was the potentially incorrect answers to the use of the self-selection. The question -- if one interpreted the answer to saying, "Well, no, I wouldn't use it because I don't have an allergic rhinitis episode right now," that's a correct answer.

The other is actually a speculative answer. The question then would say, well, what about the people who didn't answer that correctly? What did these folks answer? And in looking at the answers, the answers essentially were speculative. "Well, if I had allergic rhinitis, I would use it, but I

wouldn't use it for asthma."

I can't tell you specifically how each one of these was interpreted, but that seems to be the flavor of how this sort of thing was interpreted.

DR. HEMWALL: Dr. Gould?

DR. GOULD: Yes?

DR. HEMWALL: Perhaps it would be best to answer the question about how we look at the lower bound of the confidence interval and how that relates to the point estimate in an observational study. And I'll have Ms. Arya talk about how we actually went through this, which was an a priori defined mitigation in this particular --

DR. GOULD: That was about what I was going to suggest, but I was responding to the question.

DR. HEMWALL: Okay.

DR. GOULD: The third point had to do with the boundaries of the confidence intervals in an observational study. As Ms. Arya pointed out, the 90 percent lower bound, or lower 95 percent confidence bound, was quite arbitrary. And that's simply saying you would expect no more than

about -- since it's a two-sided bound, no more than about 2 and a half percent of the respondents to be -- essentially no more than 2 and a half percent to be incorrect.

That again --

DR. D'AGOSTINO: No, it doesn't say that. It says that you have a 95 percent confidence that the population percent -- it's not 2 and a half percent would do it incorrectly. It said the data's consistent with the 90 percent of the population doing it correctly and 10 percent not doing it correctly.

DR. GOULD: Well --

DR. D'AGOSTINO: It's a confidence interval on a proportion, not a tolerance --

DR. GOULD: Well, that's whether it's a one-sided or two-sided confidence interval.

DR. PARKER: Let's go at this point --

DR. HEMWALL: I think another way of looking at this is very simple, and I think Barbara Cohen would also mention this in her discussion. The lower bound of the confidence interval is meant to

understand what the worst case scenario might be from the point estimate that we see in the study. So it's not meant to define that the study has passed/failed on some rigorous, up one side or the other of the 90 percent, but just understand what would actually be the worst case in terms of the power of the study to determine that confidence interval.

Now, the other question was about what we did in that particular study. And I'm going to try to be brief -- and hopefully I can cover it without bringing Ms. Arya to the table -- is that we knew that -- and we know this from our understanding of the category, that some people with asthma also suffer from allergy symptoms. But when we recruited for the study, we asked people if they had asthma only, and they said they did. But when they read the product label and saw that it treated these other symptoms, they said I can use this. And we got that information from them, and we defined a priori that that would be correct if they gave that information.

So that's what you're seeing here, is the people who stated they had asthma only, but turned out, oh, yeah, I do have allergy symptoms, runny nose, and this would work for me if I used it, and that's why we made that mitigation.

DR. D'AGOSTINO: Do you know that beforehand that you're getting a lot of wrong responses and let me scratch my head and try to figure out why?

DR. HEMWALL: No. We knew that would happen beforehand, and we defined it beforehand.

DR. PARKER: Great. So we'll move on to Dr. Kramer. Thank you.

DR. KRAMER: I have a question for Dr. Stoloff. I'd like some clarification on slide C-74. In that slide, you talk about multiple studies identifying montelukast with controller medication, resulting in improvement of symptoms. Are you talking about studies that showed a statistically significant additive effect?

DR. STOLOFF: Yes, ma'am.

DR. KRAMER: I did not see any sign of any studies in the packet that showed an additive

effect of this drug on top of other medications. In fact, if anything, the comparisons I saw showed less effect compared even to antihistamines.

So this was specifically -- could you clarify? Are these asthma studies?

DR. STOLOFF: These are asthma studies.

DR. KRAMER: I think if there were studies showing superiority with this drug, it would have been nice to see the studies, and to just see it as a comment and opinion was not adequate.

Secondly, actually this is a question for an earlier speaker. Slide 33 concerned me. I guess it was Dr. Bissonnette. And on that slide, where you're talking about overall safety, it concerns me when we have blanket statements that the adverse event profile is comparable to placebo, that there's no statement of the limitations of these studies in terms of duration, the lack of active questioning for things that have subsequently been found to be of concern in terms of neurospsychiatric side effects. So I just think having statement "this is safe" and "it's the same

as placebo" is not tolerable without limitation of the study.

DR. HEMWALL: That's a fair point. It was in the clinical studies for allergic rhinitis that this comparable placebo safety profile was observed, and we showed you that slide. Admittedly, those studies are shorter, but the studies that were done for the asthma indications also had very similar safety profiles but more serious adverse events because of the asthma population.

I can ask Dr. George Philip to talk about the longer exposure seen in those studies, which I think are, at least in terms of the safety, transferable to what we're talking about today.

DR. KRAMER: Except you talk about longer term, but the data suggests only 250 patients received it for a year. So we're not talking about really long-term studies. We're talking about a matter of weeks.

DR. HEMWALL: That's right. And so now we're also talking about the 66-million

patient-years of exposure in actual use over the last 16 years, where there are hundreds, thousands of patients that probably -- I can't even imagine what the exact number is -- have been taking this chronically for many years.

DR. PARKER: Okay. We have a long list of people who are on the queue. Let me encourage those on the committee to frame your questions as clearly as you can, directly, so that we can move toward getting responses to them; the art and science of questions, asking, and answering, I know, since there are also many points for discussion.

Ms. Pledge, please.

MS. PLEDGE: Well, I have real simple ones. You said that Singulair was one of the top ten prescribed medications. Was that also for adults and children or just adults?

DR. HEMWALL: It's across the board. It's used widely in adults and children.

MS. PLEDGE: Okay. Did I also hear that the drug has ephedrine in it?

DR. HEMWALL: The drug does not have any other ingredient. Montelukast is the only ingredient. The point was being made that it reduces congestion, which pseudoephedrine also does.

MS. PLEDGE: Are the most side effects noticed after the first dose or after several doses?

DR. HEMWALL: There's no dose relationship when side effects are reported.

MS. PLEDGE: Okay.

DR. HEMWALL: And in the clinical trials where we have the opportunity to actually look at that and collect the information with a temporal association, the time frame -- there is no time frame. And the adverse events are low compared to placebo.

MS. PLEDGE: How quickly does Singulair work?

DR. HEMWALL: Singular has been shown in the allergic rhinitis trials to work on the first day of treatment. And that effect increases over time.

In exercise-induced bronchoconstriction, the instructions on the label are to take it at least 2 hours before exercising. So the inference there is that the effect could occur as early as 2 hours.

MS. PLEDGE: My last question is, there is a focus on age groups, each of the age groups. What if you had a patient that was either grossly over- or underweight but in that certain age group, would you still prescribe that dose?

DR. HEMWALL: That's a decision that would be made by a physician, and I think physicians are often accustomed to looking at a child that maybe had a higher wait or had an early growth spurt. We might consider giving a higher dose to a child.

We're talking about adult dose here today, but the good thing about this product is that it's safe, and shown to be safe, in many multiples of therapeutic doses. So an error in that regard would not have a clinical consequence.

MS. PLEDGE: Okay. Thank you.

DR. PARKER: I want to re-ask one of those questions. I think I heard the answer a certain

way, and I just wanted to see if we have more information.

It is one of the top ten prescribed medications across ages. Could you tell us where it falls for the pediatric population and also where it falls for the adult population? Are those the same or are they different, just as a baseline for knowing who's currently taking it?

DR. HEMWALL: I'm not sure we have that exact information, and I know we have access to it, though. And we could get that for you after the break. The adult population is, by inference, larger, so I think you're going to see larger. But it is widely used in pediatric populations.

DR. HEMWALL: Next on the cue, Dr. Gerhard? I'm sorry if I mis-said your name. Help me.

DR. GERHARD: This is Toby Gerhard. Hello. A question I believe for Ms. Arya, and going back to slide 51, if possible. And basically just trying to follow up, could you maybe -- as you give on the next slide 52 where you gave a couple of verbatim answers that demonstrated what these

correct answers after initial potentially incorrect self-selection were, could you give a couple of examples how roughly 10 percent of patients that incorrectly self-identified for use with montelukast, what their responses were and what they intended to use the drug for?

DR. HEMWALL: So, Dr. Gerhard, you're specifically interested in that 9.3 that were incorrect, what were they thinking?

DR. GERHARD: Yes.

DR. HEMWALL: Okay. Ms. Arya?

MS. ARYA: So given that if we look at the numbers here, it actually boils down to only about 13 people who were incorrect out of the 151 that we started with. So it was difficult to establish any patterns there in terms of what they said, given that the sample size was very small. But I can try to find out for you, perhaps after the break, to give you an example of what a couple of those verbatims might be.

MS. GERHARD: I understand completely that this is very qualitative, but just to get an idea.

MS. ARYA: Yes, absolutely. I can get those after the break.

DR. HEMWALL: I think the important thing, what we're trying to get across today, is that there's never going to be a hundred percent correct selection in the real world. And what we're attempting to do with these studies is to make sure that our message is getting across to the wide, vast majority of the users, and we have successfully done that.

Then you have to think about what are the consequences of being wrong and what would be bad if a person who had asthma took this product despite all of these warnings. And that's why we had Dr. Stoloff try to put that part of it into perspective, because no label for any product would ever achieve that 100 percent-like type of compliance.

You need to sort of think about it the same way you would are you concerned that a person taking an NSAID might also decide to treat their own osteoarthritis, or a person taking a proton

pump inhibitor might decide to treat their erosive esophagitis with Barrett's esophagus. Those things happen right now in the real world, but we label against it, and we've actually taken a prospective -- or proactive labeling in the case of Singulair.

DR. PARKER: So great. So we are asking for information on what incorrect looks like in the N equals 13, I think what the last question -- and maybe you can get back to us with that.

Dr. Pisarik is next on the cue. Thank you.

DR. PISARIK: I just have questions regarding the whole process of mitigation in general. According to the FDA guidance, it's basically supposed to be just if somebody's on the borderline between being correct and incorrect that you might shift them to the correct column.

For instance, the adolescent question, the initial percentage correct for self-selection was actually 57 percent, so 1 out of 2 adolescents would think that they could use the medication on their own. It was only because somebody asked them

some questions, including one that said, "If use of this product would be okay for you to use, would you be more likely to take this on your own or ask somebody first?"

I mean, that's kind of a leading question there just from the get-go. But my interpretation of mitigation is basically having a learned individual there basically guiding them into the correct answer. So if this product was out on the shelves, what would keep an adolescent from using it if 1 out of 2 said that they would take it?

DR. HEMWALL: Well, we're not -- and I would think that many of us are probably not concerned with an adolescent going to the supermarket or the pharmacy and buying their own medicine. But what I think we can agree on, we're more concerned that an adolescent might find it in the medicine cabinet in the house, and read the label, and decide or ask a parent whether or not to use the product. This 84 percent with appropriate predefined mitigation was we think a pretty good score for adolescents. If you have teenagers, getting this type of

information is difficult.

Then, as I said before without trying to go overboard on my response, the clinical concern of them using it is minimal because it's already safe and effective for that age group. So we tried to create a buffer between the 18, where the cutoff is, and that's actually safe down to three years below that.

DR. PARKER: Dr. Platts-Mill, we're back to you.

DR. PLATTS-MILL: On slide 54, looking at the labeling, "This product is only for allergies. Do not use to treat asthma." So the question, which I didn't see you address, is what happens if you have a patient who is stable and taking Singulair, and they see this sign? Is it a danger that they'll stop taking their medicine if they have asthma?

DR. HEMWALL: Yes. We thought about that very carefully, and, in fact, that's why we have the other warning in the label that says do not stop taking your other asthma medications. And

consumers -- it's not all that well understood sometimes by people that don't follow the consumer marketplace, but they're looking at the product as Singulair Allergy. This is an allergy treatment. So they're not thinking about it as something for asthma to begin with. We've taken the extra step.

DR. PARKER: So I want to follow up on that. That was one of the questions I had. In the SOLID study, specifically, among the cohort that had experience with Singulair, I wanted to know how many were currently taking it that remained in the study and what they said.

DR. HEMWALL: We don't know how many were currently taking it.

DR. PARKER: That was not a part of the questioning in the study.

DR. HEMWALL: No. We asked --

DR. PARKER: Do you have any experience --

(Crosstalk.)

DR. HEMWALL: -- if they had -- had some ever taken Singulair in the past. And we wanted to cast a wide net because it could be any different

set of circumstances in which people might have Singulair experience.

DR. PARKER: So just to be clear, there is no data on those who are currently taking it for asthma and how they respond to taking it for allergies, based on the product label, just to get clarity on that point.

DR. HEMWALL: Yes. We would not expect people --

DR. PARKER: We don't have that data.

DR. HEMWALL: -- who are already taking it for asthma to buy the same product and start taking it for allergy as well.

DR. PLATT-MILLS: Right. So among the asthmatics, there are clearly people who respond well to Singulair and people who don't respond -- they make very little response. Raison [ph] has beautiful studies separating, breaking them out.

So the question is, how much does the experience with asthma correlate with effectiveness in allergies? Though I would point out that the

word "allergies" is wonderfully vague and has never been defined. And patients walk into the clinic with -- they say, "Oh, it cures my allergies. My allergies are fine, Doctor." And then you have to spend half an hour of discovering what they mean by the word. But we will forgive you for that.

DR. HEMWALL: So your question is about how different patients respond with regard to this product. I'm going to ask Dr. Allan Luskin --

DR. PLATT-MILLS: I mean, clearly there are patients who respond well to Singulair in their asthma, and some people who say it's actually much their best drug, and other patients where it doesn't seem to have an effect, and that's been --

DR. HEMWALL: Certainly.

DR. PLATT-MILLS: -- are the same categories, then, people responding well with their rhinitis?

DR. HEMWALL: You can come up here, Dr. Luskin, if that microphone isn't working.

DR. LUSKIN: Thank you. I'm Dr. Allan Luskin, University of Wisconsin. And in response

to Dr. Platts-Mills question, there is no data looking at responders for asthma to see if those are the same people who respond or don't respond to the use of montelukast in their nose or eyes, but the same phenomenon is clearly noted in nose and eyes.

There was a study that was done comparing placebo loratadine and montelukast for the eye. And what that study showed was that about 25 percent of either of the active ingredients, loratadine or montelukast, failed to elicit any significant improvement in daytime eye symptom scores. About 35 percent of both of those active ingredients had a statistically but what I would call clinically not particularly robust response. And about 40 percent of patients responded to both of those active ingredients.

But clinical experience tells us that those aren't the same people, so, to me, what's really important is that this is illustrative of what we see with virtually every other pharmacologic therapy that we have for a variety of conditions,

is that we have responders and non-responders, and that the different mode of action of this product really is the crux of the matter.

It is likely that people who do not respond to antihistamines may respond to leukotriene receptor antagonists so that we have responders, and as you pointed out, we have non-responders. And it's about a quarter, a third, and about 40 percent, and those may not be the same people. And that's what clinically is important to me, is that we have another option for those people who don't respond as favorably as they would like.

There is data in the meta-analysis that was referred to earlier, that when it comes to eye disease, that the two together are better than either agent alone, the two together being antihistamines and leukotriene receptor antagonists. While this was not seen with nasal disease, it certainly has been seen with ocular disease.

DR. PARKER: Okay. We're going to move on. I'm southern, so it's hard for me to interrupt

people. My grandmothers taught me well, but I'm going to try to keep us moving here. Bless my grandmothers.

Dr. Ownby. Thank you.

DR. OWNBY: Thank you. Dennis Ownby. I have two questions. I'll take the easy one first, and this refers to the studies of consumer understanding. And there were either 163 or 151 low literacy individuals. And I'd like to know what the definition of low literacy was, considering, in my population, 20 to 30 percent are functionally illiterate.

DR. HEMWALL: We apply a standard test that's used for all studies of this type. It's called the REALM test, which is something that can be applied fairly quickly in a study setting. And it's a test of medical health literacy. And then those who reach below a certain score on that are defined as low literacy.

DR. OWNBY: I'm familiar with the REALM. I take it this was only in the adults that it was used or did you also use the adolescent REALM?

DR. HEMWALL: We used it in the adolescents as well.

DR. OWNBY: And what was the level that you defined as low?

DR. HEMWALL: Ms. Arya, quickly.

MS. ARYA: In terms of the health literacy among adults, the level is if they score 60 or below out of the 66 points. And in the case of the teen, it is when they score below the current grade level they are in. So they are supposed to get a certain point, and if they score below that. And you assess that against their grade level, and if they're below that grade level, then they are treated as low literates.

DR. PARKER: Dr. Towbin?

DR. OWNBY: Can I ask my second question?

DR. HEMWALL: I apologize.

DR. OWNBY: This is going to slide 28 or 30 on the ocular symptoms. The statistical significance is a change of 900's on this score. And I believe this is a score from zero to 12. Is that correct? That is, it's a sum from zero to 3

of

DR. HEMWALL: A 4-point scale.

DR. OWNBY: Pardon?

DR. HEMWALL: A 4-point scale, from zero to 3.

DR. OWNBY: The total daytime score is not the sum of the individual; it's only zero to 4?

DR. HEMWALL: Dr. Bissonnette?

DR. BISSONNETTE: Stephane Bissonnette. The scale that we used during the entire development program for allergic rhinitis is a scale of zero to 3, a 4-point scale. And it's the average of those points and not the sum of those points.

DR. OWNBY: Okay. So it's the average of the scales, of the four subscales?

DR. BISSONNETTE: Yes.

DR. OWNBY: I wonder if you have ever predefined what you think is a clinically significant difference and what percent of patients achieve that clinically significant difference, going back to Dr. Luskin's comments. Because I would argue that 900ths of a change on a zero to 4

scale is hard to imagine as clinically significant.

DR. BISSONNETTE: I think that there are two parts of your questions, is the actual what as predefined as what can be clinically significant for those specific symptoms. Again, we need to remember that this Daytime Eye Symptom Score was a secondary endpoint and was not the primary endpoint of those studies. And the primary endpoint, what we will be looking for as what will be clinically significant, was a change of .12 in the allergic rhinitis studies. But again, there was no prespecified change based on the secondary endpoint.

Your second part of the question, the clinical relevance and all this, we need to take the totality of the information available to us to see how it is clinically relevant for the patient. It's actually the patient who's telling us throughout the entire development program when they scored their own systems. And we see that on those individual studies during the entire development program, as well as when we pooled those pivotal

trials. This is on one aspect. The other one is the burden of those symptoms by their patients themselves is very important. So the quality of life is also very important.

DR. OWNBY: But you're asking for a new indication for specifically ocular symptoms and not the totality of symptoms, is that correct, in this over-the-counter switch?

DR. HEMWALL: We're asking to have that included in the symptoms that are already part of the approved indication. And you've seen there are some discussions about whether or not that is strong enough to merit that. And we've also compared it to what we've seen in other products that use different endpoints in earlier years that we're able to get the itchy, watery eyes claim in their OTC labels.

DR. PARKER: So I think we heard that we don't know if that has clinical significance. I think that's what I heard. So let's move on here to Dr. Towbin.

DR. TOWBIN: Thank you. Kenneth Towbin. I

believe that one of the concerns before the committee has to do with neuropsychiatric conditions, adverse events. And I'd like to look at slide 33 for a moment, where you speak to the well-established safety. And this follows up on Dr. Kramer's earlier comment.

When you say that there were no serious drug-related adverse events in any of these studies, I'd like to know what methods were used to assess for neuropsychiatric ill effects beyond suicide. I believe that would have been something that would have surfaced right away. But I'd like to know what methods were used to look for things like mood changes, depression, sleep difficulties, and changes in thinking in these clinical trials. Thank you.

DR. HEMWALL: That might be a long answer. If I ask --

DR. PARKER: But it's not going to be. Thank you.

(Laughter.)

DR. HEMWALL: I'm going to ask Dr. George

Philip to just explain how these trials were looked at in a publication that's in your briefing book, where all the clinical trials were looked at collectively and the approach.

Please try to be brief, Dr. Philip.

DR. PARKER: And I'm going to ask you to do it in two minutes, and then we're going to take a break. And we have two more on the queue, and we're going to let them speak briefly before we move on to the FDA presentation, and I'm counting. Thank you.

DR. PHILIP: Very good. George Philip, Merck Research labs. I will keep this brief. What you're asking about is a question based on our clinical trials experience. These clinical trials were designed to demonstrate efficacy in asthma and allergic rhinitis and safety assessments as well. The safety assessments were standard for these types of development studies; that is, open-ended questions, asking patients how they were feeling compared to how they had felt previously, did they notice any changes. There were no specific

questions calling out neuropsychiatric symptoms.

DR. TOWBIN: Thank you very much.

DR. PARKER: Thank you for your answer that came in under two minutes.

(Laughter.)

DR. PARKER: So at this point, let me just let you know that we do have two more committee members on the advisory that are on the queue. Dr. Roumie, Dr. Tracy, we're going to come back to you after the break and let you ask your very clear questions and get the pointed responses so we don't get off schedule here.

We will now have a 15-minute break, and we will start right back on time in 15 minutes. Thank you very much.

(Whereupon, a recess was taken.)

DR. PARKER: This is your 30-second warning. We're about to begin. If you can join us please. Thank you.

What we'll do here as we gather, we're going to take the last two questions that I know we are mastering the art of asking and answering targeted

questions here so that we can hear from everyone. We've got two committee members that we'll call upon, Dr. Roumie and Dr. Tracy. And then we'll move right into the FDA presentation. Thank you all.

Dr. Roumie?

DR. ROUMIE: Christianne Roumie. My question is actually related to the Drug Facts label. I didn't see any limitation on duration of use. And given that most of the seasonal allergic rhinitis trials were, at most, 4 weeks, and the perennial ones were 6 weeks, I didn't know whether or not a stop if your symptoms don't improve in 7 days or something like that was included.

DR. HEMWALL: And actually, this is not specified on any of the projects for allergic rhinitis because consumers are expected to use the product for as long as they have symptoms, whether it be for the season or for longer periods. And that's what we've stated on the label, to only use it during the time you have symptoms.

DR. ROUMIE: I believe that -- I think the

nasal steroids had a stop if your symptoms don't improve in 2 weeks, or do not use for more than 2 weeks.

DR. HEMWALL: And we're patterning ours off of the oral products, the antihistamines, which is the labeling for antihistamines. So your point is taken.

DR. PARKER: Thank you. And I might also ask, as I know often happens, if you could also please provide us both with the Drug Facts label and also the consumer information leaflet to take a look at physically and just make those available to use at lunch time; put those around.

DR. HEMWALL: We are ready to do that.

DR. PARKER: I knew you would be. Thank you so much.

Dr. Tracy?

DR. TRACY: Yes, Jim Tracy. This question is for Dr. Stoloff. He made a comment about potential off-label usage. And I was wondering, if I understood you correctly, were you suggesting that off-label usage may have potential or good

benefits? And if so, could you elaborate on that?

DR. STOLOFF: Thank you for the question. Dr. Stoloff. No, I am not suggesting, under any form, off-label use. However, there is data that when the medication is used, it works in certain patients, as has already been discussed by Dr. Luskin, for patients with asthma and allergic rhinitis. But under no circumstance am I recommending it be used or suggesting that it be used for off-label use.

DR. PARKER: Thank you. We'll move right on into the FDA presentation. Thank you.

FDA Presentation - Erika Torjusen

DR. TORJUSEN: Good morning. My name is Erica Torjusen. I'm an allergist-immunologist and medical officer with the FDA in the Division of Pulmonary Allergy and Rheumatology Products. And I will be presenting the clinical trial data, which led to the approval of montelukast for prescription use. I would like to thank Dr. Parker and members of the Nonprescription Drugs Advisory Committee for being here today to share your expertise.

This is an overview of my presentation. First I will provide an overview of the regulatory interactions that have taken place between the sponsor and the agency. This will be followed by a reminder of the indications and dosing for montelukast. Next I'll provide a brief summary of the efficacy data that led to montelukast prescription approval, followed by data from previously conducted studies that have been resubmitted in support of a new claim regarding the relief of eye symptoms.

With the exception of the new eye claim, efficacy was already established during the prescription approval process, therefore I will quickly review the efficacy information before moving on to safety considerations. This will include a discussion of common adverse events and the warnings and precaution statements included in the current product labeling for neuropsychiatric events and eosinophilic conditions.

I will then close with considerations regarding the treatment of allergic rhinitis in

both the prescription and OTC arenas. My presentation will focus on data obtained from clinical trials, while other FDA presentations will provide a review of the postmarketing safety data.

This slide summarizes the interactions held between the agency and the sponsor prior to submission of this partial OTC switch application. During an initial meeting, the agency expressed concern that a partial switch for allergic rhinitis, or AR, could result in inappropriate treatment of bronchospasm by consumers with potentially serious adverse consequences, given the prescription indications include an exercise-induced bronchoconstriction.

During a subsequent interaction, the agency addressed three main points. A new eye claim would need to be supported by substantial evidence of efficacy. The OTC label must warn consumers about neuropsychiatric events, and this warning should be included in the labeling comprehension studies. Finally, the concern regarding consumers taking another montelukast product along with Singulair

Allergy should be addressed.

As you heard from Dr. Michele earlier this morning, the treatment of allergic rhinitis has already been established as an over-the-counter indication. As a reminder, the slide summarizes the approved indications of montelukast for prescription use, including the age groups and doses approved for each indication.

In this application, the sponsor proposes a partial OTC switch of the 10-milligram tablet for seasonal allergic rhinitis, or SAR, and perennial allergic rhinitis, or PAR, in adults 18 years of age and older. All the other indications and dosage forms will remain prescription.

The proposed OTC indication is as follows: temporary relieves these symptoms of hay fever and other respiratory allergies: nasal congestion, runny nose, itch, watery eyes, sneezing, and itching of the nose in patients 18 years of age and older.

I will now provide a brief overview of the efficacy data that supported the prescription

approval of montelukast, in addition to a summary of the data from three previously conducted studies that have been resubmitted by the sponsor in support of the new eye claim.

This table summarizes the clinical trials that supported the approval of montelukast for SAR and PAR. Efficacy for SAR was evaluated in 8 trials conducted in patients 15 years of age and older. This included three phase 2 trials and five phase 3 trials with a large number of participants. The primary endpoint was Daytime Nasal Symptom Score or DNSS. DNSS was calculated as the mean of the individual symptoms of congestion, rhinorrhea, pruritus and sneezing, each scored on a zero to 3-point scale.

The PAR indication followed the SAR indication. Efficacy for PAR was evaluated in two large phase 3 trials in patients 15 years of age and older. The primary endpoint was DNSS, however, one trial did not include nasal itching as a component in the DNSS.

This table presents the efficacy data which

supported the approval of montelukast for the SAR indication. In summary, with a large sample size, a statistically significant difference between montelukast and placebo was demonstrated in 5 of the 8 trials.

Loratadine was included in all trials as a positive control, serving to validate the results. Although a formal comparison between montelukast and loratadine was not prespecified, inclusion of loratadine demonstrated that the mean change from baseline in the DNSS for montelukast, while statistically significant versus placebo, was numerically small and consistently less than the change noted for loratadine.

It is important to note that there is no defined minimal clinically important difference, or MCID, that is used by the agency to make decisions regarding nasal symptom scores such as DNSS, and therefore, evidence of efficacy has been based on statistically significant separation between active treatment versus placebo. Therefore, the efficacy of montelukast in the SAR clinical development

program was established.

This table summarizes the efficacy data from the two phase 3 trials which supported the approval of montelukast for the PAR indication. In Trial 246, montelukast failed to show a statistically significant difference from placebo in the primary efficacy endpoint, whereas cetirizine was statistically significantly better than placebo.

Guided by the results of the first phase 3 trial, the sponsor conducted a second trial, 265. The design and conduct of this trial was similar to 246 with two notable exceptions. First, nasal itching was removed from the DNSS because in Trial 246, there was no numerical effect on nasal itching score for montelukast; and second, no active comparator was included. In Trial 265, montelukast was statistically significantly superior to placebo for the primary efficacy endpoint.

In summary, the clinical development program supported the efficacy of montelukast in the treatment of PAR, however, the sample size was

large and the treatment effect size of montelukast was small, as was seen in the SAR program.

The current montelukast prescription label describes efficacy related to nasal symptoms of allergic rhinitis and does not include a claim for the relief of eye symptoms. As part of this partial OTC switch, the sponsor proposes to add an indication for the relief of itchy, watery eyes.

Data from three previously reviewed SAR trials were resubmitted to support this claim. In each trial, the Daytime Eye Symptom Score, or DESS, was a secondary endpoint that was defined as the average of teary, itchy, red and puffy eyes, each scored on a zero to 3-point scale.

This table summarizes the results of these three trials. When correcting post hoc for multiple comparisons, the p-value is only significant in one trial, Trial 162. In addition, the treatment effect sizes are small and of questionable clinical significance. Overall, the data does not demonstrate substantial evidence of efficacy.

I will now move on to a discussion of safety data from the clinical trials and safety issues of interest. The safety data for montelukast is comprised of both the clinical trial data as well as postmarketing data obtained since its approval in 1998. My presentation will focus on the clinical trial data, and subsequent FDA presentations will present the postmarketing experience.

As seen in this table, the premarketing safety database was large. Note that the long-term safety data was from the asthma program. The SAR and PAR development programs each had a large number of patients but short durations of exposure.

In the SAR program, upper respiratory infection was the only adverse reaction reported, with a frequency of greater than or equal to 1 percent and at an incidence greater than placebo. In the PAR program, sinusitis, upper respiratory infection, sinus headache, cough, epistaxis, and increased ALT were adverse reactions that occurred with a frequency of greater than or equal to

1 percent and at an incidence greater than placebo. These findings were consistent with the overall safety database, including all approved montelukast indications.

While the focus of my presentation is on the clinical trial data, I want to introduce two safety issues of interest that were identified postmarketing and resulted in a post-approval review of clinical trial data. The first issue is neuropsychiatric events.

In 2008, the agency initiated a safety review of drugs that act via the leukotriene pathway for a potential association with neuropsychiatric events, including suicide. This review was initiated due to requests from the sponsor to update the montelukast package insert to include neuropsychiatric events and a report of a suicide in an adolescent male taking montelukast in the fall of 2007.

As a result, the agency issued an early drug safety communication in March of 2008 regarding the ongoing safety review. The agency requested that

sponsors evaluate the safety data from the clinical trials. Merck identified 41 trials for review with a large number of patients as shown. Most of these trials were conducted in patients with asthma.

During this review, one case of suicidal ideation was identified in the montelukast treated patients with an incidence of 0.01 percent. The frequency of behavior-related adverse events was 2.56 percent in the montelukast treated patients and 2.12 percent in placebo patients. Sleep disorders were the most common behavior-related adverse events in adults. The incidence among 18 to 30 year olds was 0.91 percent for montelukast treated patients and 0.38 percent for placebo patients.

In conclusion, a strong signal for neuropsychiatric events was not identified in the clinical database. The overall rate of behavior and mood-related events was low, with sleep disorders being the most common in adult patients. However, the agency acknowledged the limitations of the clinical trial data because the clinical trials

were not designed specifically to examine neuropsychiatric events, and many of the trials were of short duration. Despite these limitations, the agency requested that the sponsor add information to the montelukast product label regarding neuropsychiatric events.

Churg-Strauss syndrome or CSS is the other safety issue of interest that I will introduce. It is also listed in the warnings and precaution statements and is defined as a vasculitis of the small to medium-sized arteries. The diagnostic criteria are listed.

The potential association of leukotriene receptor antagonists and vasculitis, including CSS, is well recognized. In February 1998, during the initial approval of montelukast, information regarding the potential for CSS was included in the product label. In October of 1998, a labeling supplement was submitted by the sponsor to update the language in the product label based upon postmarketing reports.

While eosinophilic conditions such as CSS

have been reported with montelukast, these events are primarily noted in patients with asthma and no safety signal was identified in the clinical trial database.

I will now close with some considerations regarding the treatment of allergic rhinitis. As this is a partial OTC switch, the applicant is not seeking an OTC indication for asthma. This partial switch raises potential challenges associated with targeting the AR population while excluding the off label OTC use among asthmatics. This is of particular importance given the significant overlap between these two populations.

It is estimated that 10 to 40 percent of patients with AR also have asthma, and these numbers are even higher when looking at the number of asthmatics with AR, which is up to 90 percent. Therefore, it may be difficult to address these as distinct populations for the purposes of OTC labeling, and the potential for off-label use in patients with asthma presents an issue that will warrant the committee's consideration.

AR is a well established OTC indication, and there are many products available for this indication. With a number of treatment options available, it is important to review how each of these therapies fits into the clinical landscape when healthcare providers are treating AR. Each of these products has a different role in the treatment of AR based on their relative efficacy and safety profiles, and the recommended use is described in a number of practice parameters and guidelines.

Intranasal corticosteroids are considered to be the most effective for controlling symptoms and are considered to be first-line therapy for moderate to severe AR with second generation antihistamines, generally preferred for the treatment of mild AR. Intranasal corticosteroids can also be combined with second generation oral antihistamines for persistent symptoms. Leukotriene inhibitors such as montelukast are often thought of as add-on therapy for resistant nasal symptoms and for use in patients with

concomitant AR and asthma.

I have provided a brief overview of these practice recommendations as background for discussion, however, it is important to keep in mind that this information pertains to the practice of medicine and may not necessarily apply in an OTC setting. Whether the management of AR in the face of multiple treatment options is relevant to the OTC consumer is an issue that we ask the committee to consider.

In summary, no new safety signals were identified during the review of the clinical trial data. Given that this is a partial OTC switch for AR in adults, there was a potential challenge associated with targeting the AR population while excluding off-label OTC use among the asthmatic population as there is significant overlap between these two populations. Therefore, potential for off-label OTC use in asthma is an important issue for discussion.

While no new safety concerns were identified in the clinical trial database, 15 years of

postmarketing experience has raised safety concerns associated with neuropsychiatric events and CSS. These concerns will be discussed in detail in subsequent presentations by the FDA.

Thank you for your attention. This concludes my presentation of the clinical trial data for the FDA.

FDA Presentation - Linda Hu

DR. HU: Good morning. I'm Linda Hu. I'm a medical officer in the Division of Nonprescription Clinical Evaluation, and I'm going to present an overview of the postmarketing safety experience of montelukast.

The topics I'm going to cover are the Merck pharmacovigilance database called MARRS, the FDA database or FAERS as reported by Merck, and the World Health Organization database or VigiBase. These are spontaneous reporting databases, and I will discuss the data presented in a sponsor submission. Then I will focus on neuropsychiatric events and Churg-Strauss syndrome.

Postmarketing data is useful to find safety

signals that may not be picked up in clinical trials because they are not large enough or long enough. However, there are some limitations in interpreting postmarketing data. Postmarketing reports are submitted voluntarily. The magnitude of underreporting is unknown, and reporting may also be prompted by, for example, publication of case reports, agency announcements, perceived seriousness, or legal proceedings.

We don't have a precise denominator, so it is difficult to ascertain adverse event rates. Clinical information is often limited or missing, and reports don't always differentiate what disease the product was being prescribed for. All indications are included in the reporting. Causality can be difficult to determine, and there may be duplicate reports.

This is a summary table of the three safety databases. The cases captured here covered reports where montelukast is used and is not specific to the allergic rhinitis indication. The WHO cases listed above represent the non-U.S. or ex-U.S.

cases since the U.S. cases are already included in FAERS, so they were removed from the WHO numbers by the sponsor.

As you can see, there's a significant difference in the proportion and number of serious reports and the different databases. Eighty-one percent of the FAERS cases are serious, whereas 18 percent of the cases in the ex-U.S. WHO database are serious. There's also a large difference in the numbers of serious cases. For instance, there's almost double the number of serious cases in MARRS as there is in FAERS, approximately 13,000 versus 7,000 over roughly the same time period.

To explain the apparent discrepancy between the total number of adverse events reported in MARRS and FAERS, the sponsor notes that ex-U.S. non-serious and listed serious events do not have to be reported to the FDA. It is unclear whether such reports are submitted to the WHO as the sum of the 5,342 ex-U.S. cases, and the FAERS cases is still far lower than what was in the sponsor's database, and the same is true of serious events.

As such, the FAERS database contains relatively few non-serious adverse events. Additional updates were provided by the sponsor but do not affect our conclusions on the data.

The sponsor's pharmacovigilance database includes data from the first worldwide market introduction in Mexico in July of 1997 through March 2013. During this time period, Merck estimates that there were 24 billion doses distributed with an estimated 66 million patient-years of exposure.

During this time period, there were 46,527 case reports, including 95,517 adverse events. Of these, 13,346 or approximately 29 percent of cases included serious adverse events, and there were 367 deaths provided by the sponsor. Removing duplicates, the FDA found 248 deaths. In general, adverse events found in the database are described in the U.S. prescription label.

The adverse events most commonly reported are in the psychiatric disorders, general disorders, injury, poisoning, and procedural

complications, nervous system disorders, and gastrointestinal disorders, system organ classes, or SOCs.

The ten most common individually reported adverse events in these SOCs and order of frequency are listed in the table. Insomnia, aggression, nightmares, abnormal behavior, and depression were each reported more than 1500 times.

Rash was also reported frequently, 1,675 times. It is top ten adverse event, but it is not among the top five SOCs. Also commonly reported were anxiety, irritability, and suicidal ideation, which was reported 858 times. The term no adverse event was coded in reports of overdose or maternal exposure with no clinical effect.

Overall, serious adverse events largely mirrored those reported under total adverse events, except that over 50 percent were in the injury, poisoning, procedural complications SOC. In addition, about 25 percent of serious reports are in the psychiatric SOC.

The sponsor has noted that the majority of

overdose cases came from a retrospective study of pediatric overdoses in children up to 5 years of age reported to Texas Poison Control during the sixth year period 2000 to 2005. A breakdown of the serious adverse events by age, where age is known, shows that approximately 60 percent of cases occurred in patients under 18 years with 40 percent of all serious adverse events in the 2 to 5-year-old age group.

The fatal reports were classified by the reviewer after assessment of the individual MedWatch reports according to the type of event most related to the death outcome. In contrast to serious reports, which largely occurred in pediatrics, the majority of the 348 fatal reports occurred in adults.

The most frequent cause of death was suicide. Next most common in the fatal cases were abortions, either spontaneous or elective, for which the mother took montelukast during pregnancy. The third most common in the fatal cases were reports of asthma without a reported diagnosis of

Churg-Strauss. There were also 13 reports of death in Churg-Strauss cases, and there were 9 reports of death involving hepatic conditions. Of the cases for which age could be determined, over 80 percent of the fatal reports occurred in adults with over 70 percent of suicides occurring in the adult population.

Next, we'll look at the FDA database, FAERS, as reported by Merck. I'd like to focus your attention to the information in the blue boxes on the right-hand side of the slide. The tables to the left are provided for your reference.

Thirteen of the top 25 most reported adverse events in FAERS came from the psych disorders category. Depression and suicidal ideation and allergic granulomatous angiitis or Churg-Strauss, are among the top three reported adverse events. Suicide attempts also appear in the top 25 adverse events, along with asthma and headache. Pyrexia, cough, vomiting, abdominal pain, and nausea are also among the most frequently reported AEs. The FDA analysis of the FAERS database will be

presented in more detail by Dr. Volpe, who will be our next speaker.

FAERS reports related to suicide increased in 2008, which is consistent with stimulated reporting after FDA's March 2008 early communication regarding its ongoing safety review of drugs that act via the leukotriene pathway and have a potential association with neuropsychiatric events, including suicidality.

FAERS continued reporting of neuropsychiatric events after the FDA warning in 2008, as noted in the lower part of the table. The spike in completed suicide reports included events that occurred in previous years and were reported only after the communication was issued.

Next, we'll go to the WHO database. Again, please focus your attention to the blue boxes on the right side of the slide. In the WHO database, the 25 most frequently reported adverse events are listed. Among the most commonly reported events, we can note the following. Behavioral adverse events are less frequently reported than in the

other two databases.

Headache, abdominal pain, and insomnia are the top three most reported AEs. Churg-Strauss along with nightmares, aggression and depression, anxiety and hallucinations occur in the top 25 most reported events. Asthma also appears in this listing, but suicidality related terms do not appear on the list. Outside the U.S., fewer cases related to suicide were reported.

Next, to discuss topics of interest; neuropsychiatric events. A broad set of neuropsychiatric adverse events is reported that is consistent with what is in the prescription label. These neuropsychiatric events have been reported in adult, adolescent, and pediatric patients, and include agitation, aggressive behavior, depression, nightmares, hallucinations, insomnia, irritability, memory impairment, somnambulism, suicidal thinking and behavior, including suicide. The clinical details of some postmarketing reports appear consistent with a drug-induced effect.

For Churg-Strauss, the sponsor searched the

postmarketing database for Churg-Strauss with montelukast in order to assess the percentage of patients that had confirmed diagnosis of Churg-Strauss that occurred de novo with no prior symptoms and no reduction or withdrawal of corticosteroids.

Merck's review identified 339 confirmed reports of Churg-Strauss of which 293 cases reported steroid use, both oral and systemic. Of those 293 cases with reported steroid use, 42 percent reported a reduction or withdrawal of steroids. So a large fraction of the cases did not involve withdrawal of steroids or unmasking of the condition.

The same has been reported in the literature, and the sponsor has recently updated their labeling to state that Churg-Strauss is sometimes associated with a reduction of oral corticosteroid therapy. Previously, the label stated that Churg-Strauss was usually but not always associated with reduction of steroid use.

So in summary, there are high reporting

frequencies for neuropsychiatric events and Churg-Strauss syndrome. There's a continuing association between montelukast and these events. In all three postmarketing databases, neuropsychiatric events are among the most common AEs reported and include depression, aggression, irritability, nightmares, and insomnia.

In MARRS, the majority of fatal reports greater than 80 percent and suicide reports greater than 70 percent occurred in adults and are not in children. The clinical details of some reports involving montelukast appear consistent with montelukast induced neuropsychiatric effect. Whether the sponsor has adequately addressed these adverse events for marketing in the OTC setting, we leave for your discussion.

Thank you for your attention. Dr. Volpe will be our next speaker.

FDA Presentation - Carolyn Volpe

LCDR VOLPE: Good morning. My name is Carolyn Volpe, and I am a safety evaluator in the Division of Pharmacovigilance in the Office of

Surveillance and Epidemiology. I will now present the postmarketing data received by the FDA and reviewed by the Office of Surveillance and Epidemiology for montelukast.

I will provide drug utilization data and analysis. I will provide an overview of the reports in the FDA Adverse Event Reporting System, also known as FAERS. I will also discuss a brief history of neuropsychiatric events and describe the reports for neuropsychiatric events in FAERS. I will discuss selective published literature studies for suicidality with montelukast. And finally, I will describe the reports in FAERS for Churg-Strauss syndrome.

We will now look at the use of montelukast in the outpatient retail pharmacy setting. This figure shows the total number of patients receiving dispensed prescriptions for montelukast by patient age from U.S. outpatient retail pharmacies. The overall number of patients peaked in the year 2007 at approximately 7.4 million patients and remained relatively steady thereafter. There were 7 million

patients in 2013. Of these, patients 18 years and older accounted for the majority at approximately 62 percent or 4.4 million patients, followed by patients age zero to 17 years at approximately 38 percent or 2.6 million.

This graph displays the number of pediatric patients receiving dispensed montelukast prescriptions by patient age, the highest proportion of pediatric patients for those age 6 to 14 years, highlighted by the green line, followed by patients age 2 to 5 years, highlighted by the red line.

This table provides the number of patients receiving dispensed prescriptions for montelukast by patient age and drug strength for the year 2013. The majority of patients age zero to 5 years got the 4-milligram strength, while the majority of patients age 6 to 14 years got the 5-milligram strength. The majority of patients age 15 years and older got the 10-milligram strength. This is consistent with the dosing found in the montelukast prescribing information.

Of note, the proposed over-the-counter product would be available as the 10-milligram tablet and labeled for adults ages 18 years and older. There is concern that a 10-milligram over-the-counter would be inappropriately used by children and adolescents under 18 due to a lack of dosing guidelines on the packaging for this age group and perhaps prior experience using the prescription montelukast product.

We now move on to the top diagnosis associated with the use of montelukast as reported by U.S. Office-Based Physician Survey over the cumulative time period, from 2009 to 2013. The top diagnoses associated with the use of montelukast in the pediatric population were asthma at 52 percent of uses and allergic rhinitis at 27 percent of uses. In the adult population, the results are similar with asthma at 51 percent of uses and allergic rhinitis at 22 percent of uses.

We will now take a look at the FAERS data for montelukast. FAERS is the FDA's internal database which contains spontaneous postmarketing

adverse event reports for drugs and biologic products. In the previous presentation, the data submitted were submitted by Merck. I will now describe data submitted to the FDA retrieved from FAERS for montelukast and reviewed by the Office of Surveillance and Epidemiology. Although there are differences in the number of reports, similar adverse events are seen in both databases.

As of October 31, 2013, the FAERS database contained 11,649 reports for montelukast. More than half of these reports refer adults ages 18 years and older, and asthma was the most frequently reported indication. Serious outcomes as defined by CFR 314.8 -- which includes death, hospitalization, life-threatening events, disability, congenital anomaly, and other serious events -- were reported in 76 percent of reports, and neuropsychiatric events were the most frequently reported adverse events in these reports.

We will now take a closer look at neuropsychiatric adverse events with montelukast

use. As described previously, the FDA began reviewing FAERS and clinical trial data for leukotriene receptor antagonists in 2008 for a possible association with neuropsychiatric events. In addition, the FDA released an early drug safety communication in March of 2008 to announce the review of this possible association.

Due to the release of this communication and increased awareness by healthcare professionals and consumers of this possible association, the FDA received a large influx of reports for montelukast in 2008. Neuropsychiatric events now appear in the warnings and precaution section of the montelukast prescribing information.

The FDA reviewed the postmarketing reports for neuropsychiatric events with montelukast use in 2008. This case series included 400 cases of neuropsychiatric events prior to the release of the drug safety communication. Half of the cases were reported in adults 17 years and older, and asthma was the most frequently reported indication. An allergy indication was reported in 9 percent of

cases.

A abroad set of events were reported with sleep disorders and disruptive behavior most commonly reported. These cases were compelling, with 34 of the cases reporting a positive rechallenge. A case was considered a positive rechallenge if the patient developed an adverse event after taking montelukast. The event resolved after discontinuation but returned after reinitiating montelukast. The neuropsychiatric events appeared to be consistent with a drug-induced effect.

This slide shows Section 5.4 of montelukast warnings and precaution section, which discusses the neuropsychiatric events. The adverse events are bolded for emphasis and represent the neuropsychiatric events seen in the 2008 review of the FAERS data.

This slide represents reports retrieved in FAERS from the previous review in 2008 to October 31, 2013. The total number of reports retrieved were 2,430 reports. This data contains

the influx of reports seen in 2008 after the release of the early drug safety communication. Nearly half of these reports were in adults, and asthma was the most frequently reported indication. The most frequently reported events included suicide ideation, depression, and aggression. These results were similar to those seen in the 2008 review.

This slide shows the number of FAERS reports on the Y axis and corresponding year that the neuropsychiatric events occurred in those reports on the X axis. You can see by this graph the sharp increase in the number of neuropsychiatric events that were reported to occur around the time of the FDA's release of the early drug safety communication in 2008. Since 2008, reports continue to be submitted, and neuropsychiatric events continue to occur, but the number of events has decreased and remain relatively steady since 2010.

I will now discuss published literature for suicidality with montelukast use. In late 2012,

the Division of Epidemiology conducted a review of published literature on montelukast use and suicidality. The review's objectives were to evaluate a case controlled study published in 2012 and to identify any additional publications between the years 2008 and 2012. Three databases were searched with the key terms listed here and about 20 abstracts were screened. I will summarize two of the epidemiology studies reviewed and also a study conducted by the FDA.

The Jick et al. study had a cohort of almost 24,000 montelukast users identified from the United Kingdom's clinical practice research database, previously called GPRD and now known as CPRD. Suicide cases were identified by computer-recorded diagnosis codes.

The study concluded that the risk of suicide attributable to montelukast use seemed low, only 3.9 cases per 100,000 patient-years as the upper limit of the 95 percent confidence interval. However, this rate seems underestimated because the suicide rate among all treated asthma patients from

this study was well below the expected rate for the general United Kingdom population, which in 2009 was 17.5 per 100,000 population in males and 5.2 per 100,000 in females.

We are convinced that the capture of suicides by computer-recorded diagnosis in the general physician setting was incomplete. Moreover, the identified suicide cases were not validated by any other means. Finally, a third of the montelukast users received only one prescription, meaning the extent of their exposure is unknown and could have been quite short.

With data from IMS, a large, commercial, medical insurance database, the Schumock et al. study first looked at a cohort of asthma patients from which it then selected those who had an ICD-9 diagnosis code for suicide attempts. 344 cases of suicide attempts were identified, and 70 percent of these cases were in children 12 to 18 years old.

Controls are matched to each case on age, sex, geographic region, and cohort entry time. The table here shows substantial differences between

the cases and controls and their baseline risk factors for suicide attempts. Specifically, the frequency was higher among cases than control patients in previous suicide attempts, previous psychological counseling, as well as known comorbidities and medication use that increased the risk of suicide attempts.

In this case control study, after case and control identification, montelukast exposure was retrospectively determined and only a small percent, less than 7 percent of both the cases and controls, were found to be using montelukast on the event date, resulting in low statistical power for the study.

This table presents the adjusted odds ratio for current montelukast use in suicide attempts stratified by age. Overall, the study did not show an association between current montelukast use and suicide attempts. However, the adjusted odds ratio of 5 found in young adults 19 to 24 years old was not reassuring about the lack of the association.

This case control study is subject to major

limitations. First, the cases and controls were incomparable with regard to the baseline risk for suicide attempts, therefore, the observed risk could not be attributed to montelukast exposure alone. Second, the study is not powered enough to detect the risk of suicide attempts with even lower power for age subgroup analysis. Third, little is known about the completeness of claims in the validity of claims-based algorithms to identify suicide attempts.

Finally, the study results are likely subject to residual confounding since the final adjusted model did not control for key confounders, such as the use of medications known to increase the risk of suicide attempts.

FDA conducted a study to monitor the trends in antidepressant dispensing relative to montelukast initiation. A cohort of approximately 230,000 montelukast users, age less than or equal to 45 years old, were identified from a U.S. pharmacy claims database. The comparison groups were comprised of 260,000 fluticasone initiators

and 90,000 long-acting beta agonists, corticosteroid initiators.

The study found small increases in antidepressant medication dispensing after treatment initiation in all the treatment and control groups, not just the montelukast users, which does not support specific association between montelukast initiation and adverse psychiatric effects. However, the study was subject to two major limitations.

First, the incidence of depression was indirectly measured by antidepressant medication dispensing as a surrogate endpoint, but antidepressant medications are sometimes prescribed for indications other than depression. Second, reasons unrelated to montelukast use also could contribute to the observed trend of increased antidepressant dispensing.

We're going to switch topics and briefly discuss Churg-Strauss syndrome in montelukast use. As discussed earlier, Churg-Strauss syndrome is a life-threatening condition which has appeared in

the montelukast prescribing information since approval. Churg-Strauss syndrome is one of the top events reported from montelukast in FAERS. 884 reports were submitted to FAERS for approval in 1998 to October 31, 2013. The majority of reports indicated a serious outcome.

Asthma is the most frequently reported indication, which is consistent with Churg-Strauss etiology and criteria for diagnosis. Although approximately 25 percent of the reports did not report an indication, 3 percent did report hypersensitivity or allergy as the indication for montelukast.

In summary, in 2013, the pediatric population of zero to 17 years accounted for 38 percent of patients receiving montelukast prescriptions, and patients age 6 to 14 years accounted for the highest proportion of pediatric patients. Asthma was the top diagnosis associated with the use of montelukast among all patient age groups over the examined time period.

Neuropsychiatric events and Churg-Strauss

syndrome are potentially life-threatening events, although causality with montelukast use has not been confirmed, and currently no well-designed, epidemiology studies reliably quantify the risk of suicidality. Events have been reported in both adults and children. Asthma is the most frequently reported indication, however, events have been reported when montelukast has been used for allergy relief.

If montelukast is available over the counter, there is concern with inappropriate use in patients with asthma and in children. Also, it is important for our consumers to understand to be able to identify the risks with montelukast use. These concerns will be further addressed in the next presentation, which describes the consumer studies performed for this NDA. Thank you.

FDA Presentation - Barbara Cohen

MS. COHEN: Good morning. I'm Barbara Cohen, a social science reviewer with the Division of Nonprescription Clinical Evaluation. And I'm here to talk with you this morning about the

consumer studies submitted in support of the Singulair Allergy NDA.

First, an overview of what I'll be speaking about this morning. I'll start with the issues that FDA was concerned about during drug development and follow up with a brief discussion about each of the three studies conducted. Finally, I'll provide a summary of key takeaways.

The key consumer questions of concern to FDA were, 1) will the proposed OTC drug label be adequate to convey neuropsychiatric concerns to consumers; and 2) will consumers continue to use this product off label. Specifically for off-label use, I'm referring to asthma sufferers who would use the product to treat their asthma, and I'm also referring to adolescents who might make an independent choice to use the product for either their allergies or their asthma despite being below the labeled age.

In order to address the issue of neuropsychiatric labeling concerns, the sponsor conducted a label comprehension study with adults

assessing the relevant labeled warnings. I'll refer to this study as the Neuropsych study. The sponsor also looked at warning interpretation among adolescents as part of the adolescent self-selection study, and I'll touch on that very briefly as well.

Next, in order to address the concerns about potential usage under 18, the sponsor conducted the Adolescent Self-Selection study, which I'll refer to as Adolescent. Finally, the sponsor conducted the Singulair OTC Label Interpretations and Decision study, which I'll refer to by the sponsor's acronym SOLID. That study addressed the potential off-label use for asthma.

First, I'll be discussing the Neuropsych Label Comp study. The objective of this study was to assess comprehension of the two neuropsychiatric warnings on the OTC label. The general population cohort for this study was adults with allergies with and without self-reported doctor diagnoses for depression.

The specific warnings that were assessed in

this study was stop use and ask a doctor if, 1) you experience unexpected changes in behavior, thoughts, and mood, and 2) if you experience unexpected changes or problems when you sleep. Now, this study mirrored typical label comprehension methodologies and that hypothetical scenarios were used to evaluate how the subjects could apply what they read on the label to a particular situation that someone might encounter.

The question on behavior, thoughts, or mood was, "Kara is usually a calm and relaxed person. She has allergies and has been using Singulair Allergy for the past several days. She has suddenly started feeling extremely agitated and nervous. According to the label, what, if anything, should Kara do?"

Before I talk about the results here, I want to say a few words about thresholds as they relate to consumer studies. First, target thresholds are set by the sponsors a priori, and they're grounded in clinical rationale. For this study, as well as for other studies in the submission, the sponsor

set a threshold of 90 percent, which means that the lower bound of the 95 percent confidence interval for the point estimate should hopefully be 90 percent or greater.

Ninety percent is a fairly common threshold that FDA see sponsors set when there are issues of meaningful, clinical concern. The specifics of the sponsor's rationale for 90 percent for this product are provided in your background briefing packages.

Secondly, target thresholds established a priori are just that. They're targets as opposed to hard stops. So I'll be talking in this study about studies that met their threshold and studies that did not meet their threshold. If a study met its threshold, it doesn't mean that all is necessarily well. And if it didn't meet its threshold, it doesn't mean that all is necessarily lost. The threshold is more there to provide context when considering results.

To turn back to the Neuropsych study, the behavioral warning exceeded the threshold. Comprehension of stop use and ask a doctor if you

experience unexpected changes in behavior, thoughts or mood was at 97.5 percent with a lower bound of 95.3 percent. Of the 95.3 percent, 69 percent said stop use and ask a doctor, and additional 28 percent said either stop use or they said ask a doctor, which were considered correct enough by the sponsor for the purposes of understanding appropriate action that needed to be taken.

Regarding the question on sleep, this read, "Gary has allergies and has been using Singulair Allergy for the past week. He used to sleep very well, but in the past week, he's started waking up in the middle of the night with unusual nightmares. What, if anything, should Gary do?"

This had very similar comprehension results to the behavioral question. The comprehension point estimate was 97 percent with a 94.6 percent lower bound, which exceeded the threshold. Although the study results appear to demonstrate comprehension of the warnings, I want to note that the study did have some limitations.

First of all, as with all label

comprehension studies, the study did not assess whether consumers would actually read the label on their own. The methodology of these studies by its very nature directs subjects to read the label, particularly because allergy products are so commonplace, and unusual warnings are not common on them, in relief allergy sufferers might not read the label carefully before using a product.

Secondly, you'll note that in the scenario questions, there were depictions of dramatic before and after changes, going from calm and relaxed to extremely agitated and nervous, going from sleeping very well to waking up with unusual nightmares. This might have served to cue the subjects that something was wrong when answering the questions.

It's not that these scenarios were unrepresentative of what could happen, it's just that perhaps they were not completely representative because actual behavior changes could sometimes be more subtle, say if a person was not so calm to begin with, and therefore, it would be harder to assess.

Finally, in real use, consumers may not so easily ascribe behavioral changes to an OTC medicine. These scenarios cue that the product could be the cause of the problems because it's mentioned that the product has just started being used without any other extraneous detail.

In real life, situations are likely to be more complex. Because the scenarios need to be pared down for the purposes of a study, they may not be able to get adequately at all issues. This is a limitation of any study that would have a scenario, not a critique of this SOLID label comp study per se.

A brief word about the warning interpretation component of the Adolescent study that I'm going to be discussing in fuller detail now. That warning interpretation also did well with respect to subjects describing what the neuropsych warnings meant to them and what actions they would need to take if they felt differently when using the product.

Now I'll discuss the Adolescent study in

more detail. The self-selection objective here was to assess whether 15 to 17 year old would correctly choose not to take an OTC Singulair since Singulair Rx is indicated for age 15 and above.

Subjects were given the OTC label and package to read and then asked, "Is this medicine ok for you to use? Why do you say that?" If they said it was ok for them to use, they were then asked, "What, if anything, would you use this product to treat?" Again, if they said it had been ok to use, they were then asked, "You said that this product would be ok for you to use. Would you be more likely to take this on your own or would you ask someone first?"

With respect to study results, 58 percent said no, it's not appropriate for me to use, which was correct self-selection. An additional 26 percent said they would ask an adult when prompted. Therefore, the final mitigated self-selection was 84 percent, which, with a lower bound of 80 percent, was below the 90 percent a priori threshold.

Prompting the subjects to say whether they would ask an adult was one limitation of this study because it could have upwardly biased the results. The subjects knew that their parents were sitting in the next room, and some may have felt that it was the socially appropriate answer to provide. Also, this study focused on age as the appropriate self-selection criteria. It did not focus, for instance, on whether adolescents would use the product for asthma rather than allergies.

The final study that I'll discuss today is the SOLID study. This study was a hybrid, self-selection label comp study. First, subjects went through the self-selection questions, and then they were assessed for label comprehension. The objective of the self-selection component was to evaluate appropriate self-selection. And the objective of the label comp component was to evaluate the key warnings on the OTC label, "Do not use to treat asthma. If you're currently taking asthma medications, do not stop taking them," and "Children under 18, do not use."

The SOLID study consisted of 733 general population subjects with asthma. There were two cohorts, those who had ever used Singulair Rx at some point and those who had never used Singulair Rx. FDA has asked for these two separate cohorts because we wanted to assess whether those who had familiarity with the Rx product would be inclined to think it was appropriate to use OTC. Within each cohort there were two subgroups, those with indoor or outdoor allergies and those without indoor and/or outdoor allergies.

This chart more fully represents the study demographics. The key takeaway here is that for both cohorts, most subjects fell within the asthma and allergy subgroup rather than the asthma-only subgroup. The sponsor states that this is representative of the general asthma population, as published studies estimate that 80 to 90 percent suffer from allergies as well.

The self-selection component had the following protocol. Subjects had time to look at the label, and then they were asked a series of

questions: "Is this product appropriate for you to use personally or not?" "If yes, what would you use this product to treat?" "Why do you say that?" And "What led you to make that decision?"

This table presents the final sponsor reported results of the self-selection component. Before reviewing the table, I want to highlight what correct self-selection meant within the context of this study. Correct self-selection could have been, "No, it's not appropriate for me to take this product," or, "Yes, it's appropriate for me to take this product." As long as the subject stated that he or she was using it for allergies or allergy-like symptoms, it was generally assessed to be correct.

As this chart shows, for the cohort of asthma sufferers who had previously used Singulair, 91.7 percent self-selected correctly, representing a lower bound of 88.4 percent, and therefore not quite meeting the 90 percent threshold. For the cohort of asthma sufferers who had never used Singulair, this cohort had a 96 percent correct

self-selection rate, and thus they did meet the threshold.

Now this chart further illustrates how some subjects' self-selection decisions were assessed by the sponsor. The concept here is commonly referred to as mitigation in OTC consumer studies. You can see here how those in the asthma-only cohort who said they would use it, but not for allergies because they didn't have allergies, were initially characterized as incorrect. However, when asked what they would use it for, many of these subjects said they would use it for symptoms such as runny noses, sneezing, and watery eyes. The sponsor determined that since these were symptoms of allergies, the subjects' selections actually comprised correct self-selection instead of incorrect self-selection.

This is an example of mitigation. Mitigation is discussed in the FDA self-selection guidance. Generally, it refers to looking at a subject's responses to several questions to fully assess context before making a final determination

about whether the answer to one particular question was correct or incorrect. Mitigation is generally considered acceptable as long as it's transparent, meaning that FDA can independently review the data for each subject to assess whether it concurs with the rationale.

The bottom line is because the asthma-only cohorts were such a small size, and many of these subjects turned out to have allergy-like symptoms, it was difficult to quantitatively assess, in this survey, how many asthma sufferers who did not suffer from allergies or allergy-like symptoms would self-select to use the product.

There were some additional limitations of this study. The assessment of correct self-selection among asthma sufferers only focused on what indication they said they would use the product for, however, more probes would have been useful. For instance, subjects in the study were asked later on in the study what triggered their asthma, and 59 percent said outdoor allergies. It would have been useful to assess whether these

subjects thought they were treating their asthma in some way when treating their allergies.

Particularly for those who had used Singulair Rx previously, it would have been useful if these subjects thought it had been prescribed for their asthma or their allergies. There was no such question in this study. Finally, it would have been useful to ask subjects what they would have intended on doing with their asthma medications once using Singulair Allergy.

Next, I'll touch on the label comprehension component of this study. One caveat to keep in mind here is that the SOLID study was conducted before any of the other consumer studies, and at that time, the OTC draft label did not include the neuropsych warnings. It's possible that the unusual nature of the neuropsych warnings might draw attention and awareness away from the labeled statements that were assessed in this study. And therefore, some of these findings here on off-label warnings may be upwardly biased.

This table presents the results of the label

comprehension component. As you can see, for both cohorts, the threshold was not met for "do not use to treat asthma." It was met for "do not stop using asthma medicine and do not use if under 18." This slide shows how often subjects said they saw their doctors for asthma. The most common frequency was once a year or less.

In summary, the neuropsychiatric warnings were generally well understood by adults and adolescents when they're directed to look at the label. One caveat is that the scenarios described dramatic and not subtle differences in behavior. Also, consumers in real life may have more difficulty ascribing behavioral or sleep changes to an OTC medicine as opposed to other factors. Again, adolescents have some difficulties in correctly self-selecting based on the do not use under 18. Less than 60 percent selected correctly before being prompted as to whether or not they should ask a parent or other adult.

Finally, questions remain about the extent to which asthma sufferers would appropriately

self-select to use this product. How these data should be interpreted in terms of the benefit/risk of OTC use of montelukast we leave to your discussion. Thank you.

FDA Presentation - Lucie Yang

DR. YANG: Hello. My name is Lucie Yang, and I'm a clinical team leader in the Division of Nonprescription Clinical Evaluation. This morning, you have been asked to absorb a large amount of information about montelukast. The purpose of this presentation is to try to tie it all together and to provide a framework for approaching the questions to be discussed this afternoon.

This new drug application from MSD Consumer Care, or Merck, seeks approval of montelukast, proposed trade name Singulair Allergy, at a once daily dosing of 10 milligrams for over-the-counter use. In the proposed partial prescription-to-OTC switch, OTC montelukast would be labeled for only adults 18 years and older for temporary relief of symptoms due to hay fever or other respiratory allergies. Products for children and for the

indications of asthma and exercise-induced bronchoconstriction would remain prescription.

I'll first highlight the efficacy results supporting prescription approval of montelukast for SAR and PAR. The safety highlights will focus on the topics for discussion already mentioned by Dr. Michele in her opening remarks, including whether the submitted data adequately addressed in the OTC setting potential off-label use for asthma treatment, potential pediatric use, and concerns regarding neuropsychiatric events. I'll close by providing a framework for discussing the benefit/risk profile of montelukast in the OTC setting.

Now let's focus on efficacy. Nasal efficacy of montelukast has been established in the prescription setting. The OTC allergy indication is considered to be the same as for prescription use, so the sponsor does not have to reestablish nasal efficacy in the OTC setting. Nevertheless, I will remind you about the efficacy data so that you can consider it as part of the benefit/risk

determination.

In a 2007 meeting between FDA and the sponsor, FDA expressed concern -- I'm sorry. Let me go to efficacy here.

As you already heard, 4 of the 5 efficacy trials demonstrated a statistically significant reduction in the Daytime Nasal Symptom Score for montelukast compared to placebo. The effect sizes were modest, less than those for loratadine. These studies supported approval of montelukast in the prescription setting for seasonal allergic rhinitis.

For perennial allergic rhinitis, one of the two studies demonstrated a statistically significant reduction in the Daytime Nasal Symptom Score. In the other study, montelukast failed to demonstrate a statistically significant difference from placebo, although there was a numerical trend in favor of montelukast compared to placebo. Cetirizine was statistically significantly better than placebo.

In these trials, the effect size was also

modest, similar to those seen for the SAR trials. Since SAR and PAR have similar pathophysiology, only a single successful efficacy trial is required to demonstrate and establish efficacy for PAR, provided that efficacy has already been established for the seasonal allergic rhinitis indication. On this basis, montelukast was approved for perennial allergic rhinitis in the prescription setting in 2005.

Now, regarding safety, many of the issues have already been touched on by the previous presentations. I will highlight the key elements from these presentations here. I have color coded the upcoming slides so that we can keep track of the issue being focused on.

First, let's consider whether the submitted data adequately addressed the potential off-label use of OTC montelukast for asthma treatment. A topic for your consideration is the appropriateness of OTC montelukast given the possibility of off-label use for asthma treatment.

In 2007, FDA expressed concern that

off-label use of OTC montelukast for asthma treatment could potentially lead to inappropriate treatment of bronchospasm in consumers who are not under the care of a physician, potentially leading to serious adverse consequences. This concern was in part based on the significant overlap between allergic rhinitis and asthma.

As you've already heard, 10 to 40 percent of allergic rhinitis patients have asthma, and up to 90 percent of asthmatics have allergic rhinitis. In the United States, allergic rhinitis affects 30 to 60 million persons, and asthma affects over 22 million persons.

In the 2007 FDA meeting with the sponsor, FDA also expressed concern about trade name recognition because the trade name Singulair is more closely associated with the asthma indication.

As you've already heard, in office-based physician practices between 2009 and 2013, asthma was associated with montelukast use in about twice as often as the allergic rhinitis was. Due to the possibility of trade name or active ingredient

recognition, FDA required that consumer studies be performed to demonstrate appropriate self-selection and comprehension that OTC montelukast would be for allergic rhinitis and not for asthma.

The SOLID study was performed to alleviate FDA's concerns about off-label use of OTC montelukast for asthma. Subjects who self-reported to have asthma only were expected to say that they would not self-select to use Singulair Allergy personally. Of the 733 subjects in the general population of asthma sufferers, only 20 percent self-reported to have asthma only.

Although individuals who self-report to have asthma and allergies make up the majority of the asthma sufferers, in the context of this study, having both conditions increases the difficulty of determining whether self-selection for Singulair Allergy was indeed for allergies or off label for asthma.

Of note, 55 of the self-reported asthma-only sufferers, who indicated that it was appropriate to self-select to use Singulair Allergy, were

reclassified from incorrect to correct self-selection based on prespecified mitigation for referencing allergy symptoms listed on the label. This included 49 of the 141 subjects who self-reported to have asthma only.

For the primary self-selection and label comprehension objectives, the study set target threshold greater than or equal to 90 percent for the lower bound of the two-sided 95 percent confidence interval. FDA has not established any specific target threshold for consumer studies, though the strictness of the threshold generally mirrors the clinical concern.

For self-selection, the majority of subjects correctly identified appropriate use even though the subjects who had used Singulair did not meet the target threshold. For label comprehension, no cohort met the target threshold for comprehending do not use to treat asthma, although the lower bound for the general population cohort exceeded 88 percent. So at this time, there is no approved OTC controller medication for asthma. It is not

clear if consumers would use OTC montelukast to self-treat their asthma, and we leave the determination of whether or not consumers would actually do that for your consideration.

The 10-milligram tablet is the approved prescription dosing for adolescents 15 years and older for all four indications. Only the 10-milligram tablet is proposed for OTC marketing, and the OTC population would be adults 18 years and older.

This brings us to our next topic, whether the submitted data adequately addressed the potential for pediatric use. Topics for your consideration include pediatric OTC use given current pediatric prescription use, potential off-label pediatric use, and dosing if the OTC product is labeled for adults only. And given that the 10-milligram tablet is an approved prescription for adolescents 15 years and older, whether it will be appropriate to label the OTC product for adolescents 15 years and older.

As you've already heard, a substantial

portion of the prescription montelukast market is in children. Of the 2.6 million pediatric patients, the age group that has the highest proportion is the 6- to 14-year age group, followed by the 2- to 5-year age group, and then the 15-to 17-year age group.

In the consumer studies, adults met the target threshold for comprehending that Singulair Allergy is not appropriate for a 12 year old, however, many adolescents selected to use Singulair Allergy despite instructions not to use under 18 years of age. This result raises concern for inappropriate pediatric use, especially since the dosing for children younger than 15 years is reduced.

Although montelukast has a large safety margin in terms of dose, you'll note that about 60 percent of the cases with serious adverse events in Merck's internal pharmacovigilance database were in children. There were also deaths and suicide reports in children. In FDA's pharmacovigilance database, about 43 percent of the total reports

were in children, and about 50 percent of the reports with neuropsychiatric events were also in children.

This brings us to our next topic, whether the submitted data adequately addressed the concern regarding neuropsychiatric events. Topics for your consideration include whether the safety profile of montelukast is appropriate for an OTC product, and whether the proposed OTC label adequately conveys the potential neuropsychiatric events and appropriate action to take if the events are experienced.

As you heard, montelukast has a relatively benign adverse event profile in the clinical trials. However, in the postmarketing setting, there has been a broad set of neuropsychiatric adverse events. The clinical details of some postmarketing reports involving Singulair do appear consistent with a drug-induced effect, and this is in the prescription label as a warning. The prescription label also advises that patients should be instructed to notify their prescriber if

these changes occur.

As you already heard, there was a sharp increase in the number of neuropsychiatric events reported with montelukast in FAERS around the time of FDA's early drug safety communication release in March 2008. Since then, the number of reports has decreased. A similar spike was noted for the FAERS reports related to suicide with montelukast around 2008, as reported by Merck.

In the cases outside of the U.S., reported to the WHO database, not shown on this slide, there was a very modest increase in the number of suicide-related events reported around 2008, and suicide-related terms were not among the top 25 most frequently reported adverse events.

As you already heard, there is no well designed epidemiology study that reliably quantifies the risk of suicidality with montelukast. Proposing to address the neuropsychiatric event issues with labeling, the sponsor conducted two studies. In one of the studies, adults met the target threshold for

neuropsychiatric warning comprehension. As you already heard, however, it is unclear whether the adults would actually do as well if not asked to look at the label, and if the scenarios describe more subtle behavior changes. In the other study, adolescents also met the target threshold for neuropsychiatric warning interpretation.

While these studies may be reassuring, we note that the risk factors for the neuropsychiatric events is not well characterized. In addition, for subjects who had neuropsychiatric events that were associated with cognitive symptoms, it is not clear if these individuals would be able to recognize the neuropsychiatric event, stop use of the drug, and ask a doctor.

I'll now close by providing a framework for discussing the benefit/risk profile of montelukast in the OTC setting. As you consider your recommendation regarding OTC montelukast, we ask that you consider both the benefits and the risks of this product. Regarding benefit, nasal efficacy of montelukast has been established in the

prescription setting.

In the phase 3 trials that supported approval of prescription montelukast for SAR and PAR, the effect sizes were modest. Leukotriene inhibitors, including montelukast, are typically not the first-line therapy for allergic rhinitis. Regarding risk, we note that there is potential for off-label use for asthma. We also ask you to consider the potential for pediatric use, including whether the product, if approved OTC, would be appropriate to label for 15 years and older.

We also ask you to consider whether the adverse event profile is appropriate for an OTC product. And if so, whether the proposed labeling adequately conveys the potential neuropsychiatric effects and appropriate action to take if the effects were to occur.

This concludes the FDA presentation. Thank you for your attention.

Clarifying Questions

DR. PARKER: Okay. We will limit ourselves to just a few questions here in order to end at

noon and give an hour to feed our minds so that we can have great discussion and feedback as an advisory to the FDA and get to the voting. So I'm going to ask the committee members to kindly practice the art of clarity, brevity, and direct questioning as we begin with Dr. Tracy, who is fast out of the gate, I'll say.

DR. TRACY: I was last, last time, so I thought I'd get in early. Going back to the potential for off-label use, I was wondering if the agency or the sponsor had considered the possibility of a cost-conscious, resourceful mother using a pill splitter on a 10-milligram, film-coated tablet. What would that affect on absorption and maybe even disease management as they try to avoid co-pays for doctors' visits?

DR. MICHELE: That's an interesting question and not one that has come up in our discussion. As I recall, this is not a scored tablet, so we would not have looked at the distribution within the tablets specifically as part of the chemistry.

DR. PARKER: Dr. D'Agostino?

DR. D'AGOSTINO: Just a clarification from Erika on the eye claim. In your slide number 9, you give only three studies, of which one is significant and two aren't. In the sponsor's presentation, they give all five studies, all five phase 3 studies. And so they end up getting a more impressive array of significant studies.

Can you tell me why you have only three studies out of a possible five? Is it because they're pivotal studies and the other two are phase 3 but not pivotal and should not be given much weight by the committee?

DR. TORJUSEN: Thank you. This is Erika Torjusen, FDA. So the sponsor only submitted the three studies that I presented in my presentation as support for their eye claim for the OTC indication. The other two studies were submitted to the agency previously in support of the SAR indication for the original Rx indication. However, they were not submitted as part of this OTC switch in support of the eye claim. And therefore, the agency did not review the data in

these two additional studies. This is actually the first time we've seen those values presented. And being that they didn't actually pursue an eye claim in the SAR indication for their Rx label, this was really never reviewed for that specific endpoint.

DR. PARKER: Dr. Gerhard?

DR. GERHARD: Tobias Gerhard. It's a question for Dr. Volpe, or a comment, actually, regarding slide 19, maybe 20. So you mentioned -- this is regarding Schumock case control study. You mentioned or introduced the table presented here that shows the rates at baseline for previous suicide attempts and let's say bipolar disorder and depression. As a limitation of the study, there are big differences between the cases and controls.

I just wanted to clarify for the committee, as this is a case control study, these numbers do not inform our ability to look at these variables as confounders. The comparison here is between those with a suicide attempt and those without. So you obviously would expect higher rates of previous

suicide and all the established risk factors here.

In order to inform a potential assessment of confounding, you'd have to compare the montelukast users to the non-users, which is not shown here. That doesn't mean that these variables don't act as confounders. We just can't tell from the data here. So these numbers presented here certainly are not what's driving this odds ratio of 5 or greater than 5 that showed up in the greater, 19 to 24 year olds on slide 20, just for clarification.

DR. PARKER: Is there a response to that? Would you like to -- do we need to put that up or have you made the point? Or did you want a response or clarification?

Could we get the correct slide again? Because I think we're missing the exact slide if there's a reference to a slide. Which presentation? I'm sorry?

DR. LI: This is Jenni Li, FDA, OSE, DOP [ph]. Your point is well taken. You're right that this is a case control study, and the case was identified first and looked retrospectively to

identify whether the patient was exposed. This is not a perspective cohort design. However, we still want to point out this baseline difference.

DR. GERHARD: But again, the baseline difference is between patients that experienced suicide -- have committed a suicide attempt and those who didn't; not between those that took montelukast and those who didn't, which is the question that the odds ratio reflects.

DR. LI: That's correct.

DR. GERHARD: That is an important distinction. So these numbers don't -- there may be many reasons why the result shown in the Schumock study for this one age group isn't valid. But this doesn't speak directly to this question. That's I think important to point out.

DR. LI: That's right. That's a good clarification.

DR. PARKER: Ms. Pledge.

MS. PLEDGE: I have a quick one. In persons who have had a neuropsychiatric side effect, how long did it last, and did it stop with cessation of

the medication? Did they have other side effects?

LCDR VOLPE: Hi. This is Dr. Volpe. The positive rechallenge cases I presented, they did show that the neuropsychiatric effects did stop when the drug was stopped and started again when the drug was reinitiated. We also had the positive dechallenge cases that were also presented on that slide. And those cases did show that the neuropsychiatric effects resolved after the drug was discontinued.

Does that answer your question?

MS. PLEDGE: Yes. Did they also have to take medication to counteract the side effects?

LCDR VOLPE: That information I don't have.

MS. PLEDGE: Okay. I also wondered if patients who had side effects, were they already prone to have side effects to other medications?

LCDR VOLPE: I don't think we looked at that either. But we were just trying to look at the neuropsychiatric effects.

DR. PARKER: Dr. Platts-Mills?

DR. PLATTS-MILLS: Thank you. I have a

question of clarification from Dr. Hu about the 42 fatalities in relation to abortion or miscarriage. What does that mean? Is this mothers dying?

DR. HU: Excuse me?

DR. PLATTS-MILLS: Is this the mothers dying?

DR. HU: No. It was the fetus dying. So either there were spontaneous abortions or else because they were on the medication, they decided to get --

DR. PLATTS-MILLS: I've never seen a miscarriage --

DR. HU: -- an elective abortion.

DR. PLATTS-MILLS: -- classified as a fatality in that way, and I think it's very dubious.

Can I make a point in general, that prescribing Singulair, I have never warned a patient about neuropsychiatric events. And if we warned patients about any side effect that occurred in less than .1 percent, we would not prescribe any drugs at all.

I think it's a very -- we're judging these labels as if there were some extraordinary high standard for everybody understanding OTC drugs, which does not apply to prescribed drugs because most patients don't understand what we say and don't do what we say; that's for sure. I mean, the idea of 90 people saying only 90 percent understand it, it's way less than that that I understand what we say about drugs when we normally prescribe them.

DR. PARKER: Well, okay.

(Laughter.)

DR. PARKER: We will now break for lunch, and we will reconvene in this room one hour from now. That will be -- just to remind you, that will -- actually, I'm cutting three minutes. We will be back here at 1:00, at which time we will begin an open hearing session.

Please take any personal belongings you may want at this time. Panel members, please remember there should be no discussion of the meeting topic during lunch amongst yourselves and ourselves, or with any member of the audience. Thank you. After

lunch, the DFO will give a five-minute warning and ask everyone to begin taking their seats. Thank you very much. Buon appetito.

(Whereupon, at 12:03 p.m., a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

(1:02 p.m.)

Open Public Hearing

DR. PARKER: Welcome back, and we will begin our afternoon session here.

Both the FDA and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationships that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the

beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy and respect. Therefore, please speak only when recognized by the chair. Thank you for your cooperation.

We'll begin now. Will speaker number 1 step up to the podium, introduce yourself, state your name and the organization you're representing, for

the record. Thank you.

MS. MCGILL: Good afternoon. I'm Karleen McGill. I'm a board certified nurse practitioner with an allergy practice -- for Allergy Partners -- get this straight -- with Allergy Partners with central Indiana for more than 17 years.

Our practice consists of four physicians and three nurse practitioners. We are the largest practice in Marion County, Indiana. We have 10 offices in Indianapolis and surrounding areas. We treat all age ranges for allergy, asthma, clinical immunology, and food allergies. While my travel expenses are paid for by Merck, I receive no compensation for appearing before you today. I'm here to represent adult allergy patients, both in our practice and those not in our practice, who would benefit from having Singulair available over the counter.

Let me start by thinking the panel for holding this important meeting and expressing my appreciation for the opportunity to provide

comments. Approximately 10 to 40 percent of the adult population is plagued with congestion, sneezing, itchy nose, palate, eyes, ears, runny nose, and all the characteristic symptoms of allergic rhinitis.

In my experience, patients not only suffer from these symptoms but also related sleep disturbances that lead to fatigue, daytime solmnolence, irritability, and memory deficits. And this is just the tip of the iceberg. There is the economic impact of missed workdays, decreased productivity and increased healthcare costs of untreated or poorly treated allergic rhinitis and allergy.

Types of allergic rhinitis include, which we've mentioned this morning, seasonal, perennial, occupational, and episodic. Comorbidities result as a result of these symptoms, such as acute and chronic sinusitis, adult otitis media, and upper respiratory infections.

The first line of treatment is typically over-the-counter allergy medications. This

includes both sedating and non-sedating antihistamines. While several of the non-sedating antihistamines are available over the counter, they are not always able to combat all the symptoms mentioned.

Despite being classified as non-sedating, in my experience, some people are not able to tolerate them, and do sustain drowsiness, excessive dryness, or get little or no relief. It is only until they are unable to tolerate their symptoms that they seek treatment with primary care physicians or board certified allergists. Thus, some allergy sufferers have never had an opportunity to try an effective treatment like Singulair.

I have prescribed Singulair for allergic rhinitis since it was first approved, sometimes as a first-line treatment. Singulair's efficacy has proven to be great. I find it extremely safe to use. And its side effect profile is almost non-existent. I have many patients in my practice who call Singulair a miracle drug. They have excellent and complete resolution of their symptoms

by taking this drug alone.

When some of my patients heard me talking to a co-worker that I would be presenting today, they asked if they could write letters to FDA. I do not know if they did that or not. The first is an occupational hygenist from GM who suffers from seasonal allergies and finds himself traveling more due to corporate downsizing. He finds himself affected by dust mites in many of the hotels he has to stay in.

Antihistamines were too drying, and he was unable to find complete relief with other OTC agents. He has tried Singulair Allergy and has had great success. He has expressed great concern about refilling his prescriptions because of traveling, and he was glad to learn that Singulair might be available over the counter.

Another patient is an esophageal cancer survivor with allergies who found antihistamines made her too drowsy, and she didn't like the drugs interactions. Singulair has worked completely to relieve her symptoms. And by the way, her husband

is a retired pharmacist.

I also treat a Marine with allergies who doesn't want to use anything that may adversely affect him during missions. Because other drugs do not [sic] provide relief are not recommended for pilots and combatants, we tried Singulair, and it gave him relief that he was looking for without impairment. He is hoping it becomes available wherever he is stationed.

The availability of Singulair over the counter will have a tremendous positive effect on those people who suffer from untreated or poorly treated allergies. It will benefit those who only need it seasonally or episodically, along with perennial users who are routinely required to take time off from work to see a provider simply to obtain a prescription for something they know already works for them.

Providing Singulair over the counter will give these patients an extremely effective option and offers them more control of their own care. I urge you on behalf of those people who continue to

suffer from untreated or poorly treated allergies to consider making Singulair available over the counter. Thank you for convening this meeting and giving me the opportunity to comment.

DR. PARKER: Thank you. Speaker number 2?

MR. SPANGLER: I'm David Spangler with the Consumer Health Care Products Association. We represent over 80 manufacturers of nonprescription medicines of whom Merck is one. I want to talk about three themes in my five minutes; first, the value and benefit of choice among OTC medicines; second, some data points concerning responsible attitudes consumers hold towards OTC medicines as a whole; and then finally point to a number of illustrations of the same active ingredient being in both prescription and nonprescription medicines at the same time.

So first, Americans want, even demand, a range of choices among products, including medicines. This could be because of the individual variability --

(Pause.)

MR. SPANGLER: Wasn't that fun?

(Laughter.)

DR. PARKER: That was actually graceful.

MR. SPANGLER: This could be because of the individual variability and response to treatments, maybe because individual preferences vary. Some medicines in a product category could be contraindicated for certain populations, while others are not.

All of these can lead to differences in satisfaction with available treatments. And just as a point of illustration, in the allergy category, there's a wide variability in the satisfaction with any given medicine. Part of that is because of the fact that there are multiple allergy triggers. In contrast, if you want to think about a category that has fairly high satisfaction with any given medicine, heartburn would be an example.

DR. PARKER: Can you pull the mic a little bit closer? Carefully. Thank you.

MR. SPANGLER: Carefully.

(Laughter.)

MR. SPANGLER: Doing great on time.

The OTC benefit is only going to be particularly notable and grow in demand in the future. When you think about the fact that over the next decade, the allergy season is projected to lengthen by about a sixth in North America, so demand is only going to grow. There is already delays in treatment when people want to get an appointment to see their healthcare provider, and projections indicate this is only going to increase. We're going to fall short of primary care physicians by around 50,000 in the next decade.

Finally, in the value and benefit of choice in OTC medicines, there's a breadth of treatment options available in any number of OTC categories. I've listed three here: topical anesthetics, skin protectants, heartburn, as well as allergy. All of these already have nine or more active pharmaceutical ingredients for treatment.

Second, consumer attitudes towards self

medication.

Consumers report wide and high agreement with statements about how they look at and want to take control of their health. Well into the 90's agreed that I'm comfortable making treatment decisions for my minor ailments before seeking professional care; or that I prefer to find a solution for my minor ailments myself before seeking professional care; or that I prefer to treat my own ailments with an OTC before seeking professional care.

In a similar vein, you see wide agreement with statements about their confidence in their abilities to use OTC medicines. You see that they strongly agree and believe that they know that OTC medicines work from their own experience, and they believe that OTC medicines will let them take care of themselves more.

My third topic. There are many instances of the same active pharmaceutical ingredient in both prescription and OTC medicines for either different strengths or different indications. For example, ibuprofen, vH2 blockers, proton pump inhibitors,

hydrocortisone, and many others are in both prescription and nonprescription medicines. It might be because of the different indication. Those examples I just listed all have different indications for prescription versus nonprescription. Clotrimazole, oxybutynin and others would be additional examples of that.

There are also many instances of age distinctions. Smoking cessation therapy is do not use for under 18. vH2's, I mentioned earlier, are prescription and nonprescription strengths. Do not use under 12. Fexofenadine, do not use under 12. Ask a physician if you're over 65.

Another really interesting example, acetaminophen, aspirin, and caffeine as a combination, for general pain, it's ask a doctor for under 12; but for the migraine indication, it's ask a doctor for under 18. Antacids, at the older end of the spectrum, different doses for those over 60 on a number of the older antacids.

Ultimately, drawing distinctions is what labels do. This isn't unique to OTC medicines, but

that's obviously what you're considering today, and there are coexisting treatments for many, many indications.

DR. PARKER: Thank you. Speaker number 3?

MS. MAHONEY: Good afternoon. My name is Tara, and I am a physician assistant. I practice in emergency medicine in Northern Virginia. I am a member of the American Academy of Physician Assistants as well as the Virginia Academy of Physician Assistants. And I have no financial disclosures.

Today I would like to talk to you from a provider's perspective as to why I think Singulair should be approved as an over-the-counter drug for the indication of allergic rhinitis and why I feel patients are able to self-diagnose their symptoms.

So you may be thinking what role does allergic rhinitis play in emergency medicine. And truthfully, there isn't a huge role for it. But that doesn't mean I don't see it and see patients with it on a regular basis. I think many people would probably be surprised at the number of

non-emergent conditions I see and treat in the emergency room. I see patients on a daily basis for conditions that don't necessarily need emergent treatment, including those patients with allergic rhinitis.

There is what I call the convenience factor of the emergency department. Oftentimes, patients try to use a symptom, patter recognition, to more or less self-diagnose or, rather, self-identify what their symptoms are and what their body is responding to. Take someone, for example, who had previously been diagnosed with allergic rhinitis maybe by their primary care physician, at an urgent care, et cetera. So the next time they have these same, similar symptoms, they kind of attribute them to their seasonal allergies and say, okay, I know what's going on.

For allergic rhinitis, pattern recognition of their symptoms is quite obvious. The patients begin to experience symptoms of nasal congestion, rhinorrhea, itchy nose, sneezing, and watery eyes. These symptoms tend to occur in the setting of

their allergen, which has triggered this reaction. And there's often also a seasonal component to their symptoms, making it all the easier to identify.

My point is, for recurrent conditions such as allergic rhinitis, and particularly in a patient who's already previously been diagnosed with such condition by a healthcare professional, identifying their symptoms is the easy part. Obtaining treatment, however, is not quite so easy. And so this brings me back to that whole convenience factor of the ER.

So now the patient's been able to identify their symptoms, they think they know what's going on, and they want to treat it. And so what they want is typically something that's worked well for them in the past; Singulair, for example. I have patients who from time to time have been prescribed Singulair by, say, their primary care doctor, but now they're out of their prescription.

So I think that Singulair would be a great candidate as an over-the-counter drug as it's a

very benign medication -- it has a few side effects -- and it doesn't necessarily require a healthcare provider's consent for use, in my opinion.

Allergic rhinitis is most certainly a non-emergence -- although my patients may argue differently -- non-life-threatening condition that requires symptomatic treatment but is otherwise self-limited. Because patients cannot always self-treat their self-diagnosed or self-identified allergic symptoms, they must seek out a medical professional for a prescription, oftentimes being in the emergency department.

Because it's so convenient for me to see a patient after work on a Tuesday or the middle of the weekend when their doctor's office is closed, they'll come to the ER for things as simple as a refill of their prescription medication. Treating patients through the emergency department for a condition that could otherwise be safely treated with an over-the-counter medication is certainly frustrating to say the least. It's a poor use of

the time and money of our healthcare system. But truthfully, these patients still show up, regularly.

I think that other benefits of Singulair as an over-the-counter drug is that Singulair works different from other over-the-counter allergy medications, has a different mechanism of action, and for many people, it works much more effectively. Its current over-the-counter competitors, such as Allegra, Claritin, Benadryl, those types of drugs, don't always work in the same manner or as quickly as drugs like Singulair.

In terms of safety, obviously working in the emergency department, we see things such as overdose drug interactions, those types of things. I think many would argue that the overdose potential for a drug like Singulair is actually not as severe as some of its counterparts or other drugs approved already for allergic rhinitis over the counter, such as Benadryl. And then additionally, Singulair has fewer common drug interactions.

In conclusion, I ask that you carefully weigh the risks and benefits of this drug presented to you today and seriously consider approving Singulair Allergy for over-the-counter use in patients with allergic rhinitis. I'd like to thank you for your time. Thank you very much.

DR. PARKER: Thank you. Speaker number 4.

DR. KALINER: Thanks. I have no conflicts with -- no compensation with Merck. And they have funded research in my office, but I personally have not had any relationships with them.

DR. PARKER: Could you also state your name for us, please? Thank you.

DR. KALINER: Let me introduce myself. I'm Michael Kaliner, and I was the head of the allergic diseases section of the NIAID at NIH from 1975 to '93; directed the allergy and immunology training program there, amongst other responsibilities. By most standards, I had a very successful academic research career before becoming a clinical allergist-immunologist.

I left the NIH in 1993 and started the

Institute for Asthma and Allergy, which has now grown to include five, soon to be six, full-time allergists, two offices in Chevy Chase and Wheaton. Over the last 21 years, we have treated more than 58,000 new patients with allergies and currently evaluate about 4500 new patients per year. Ours is the largest allergy-immunology center in the Mid-Atlantic. I personally have treated about 10 [10,000] to 15,000 new allergy patients.

So let me address Singulair and its OTC switch from the perspective of a former academician and now a clinician. We see patients suffering from allergic diseases as one of the top two or three categories of disease for which we provide care. In my office, my first choice of treating allergic rhinitis is usually a nasal steroid, a nasal antihistamine, and sometimes an oral antihistamine.

We use Singulair, but we use it as an add-on medicine in my clinical practice, generally in those patients who also have mild asthma. As such, we see a benefit from Singulair in our patients

with allergic rhinitis. So you've seen the data about modesty in terms of its efficacy. We certainly see some efficacy in using this product.

When I considered coming here and chatting with you, I thought to myself -- I asked myself three questions. One, is there any reason why Singulair should not be available to OTC? Remember, I'm a clinician. And my answer was no. This product has proven useful. It's safe with, at least in my experience, very rare side effects. And it's not the sort of product that will be abused. I've seen a few headaches develop in patients on Singulair, but in literally thousands of users, I have not seen any major issues.

I know there's a theoretical concern about suicide. I think this concern is somewhat exaggerated. The literature's very limited regarding cases where Singulair was thought to be contributing to the suicide. And I don't want to minimize it, but I consider this not to be an important issue. Thus, on the safety side, I could not raise any major issue that would make me

hesitate to tell my patients that Singulair is now available OTC and that they might save a few dollars going to the drugstore.

How about efficacy? Well, the FDA approved Singulair for AR after reviewing a large number of trials with a lot of patients, comparing Singulair to placebo and Claritin. As I looked through these studies -- I hadn't seen them in a while -- I assessed that Singulair was effective in nasal treatment when compared to placebo about as good as Claritin, which is the leading antihistamine sold OTC. For AR, I find Singulair useful as an add-on in my practice. And in my mind, there's no doubt that clinical studies and clinical use confirm its efficacy.

So the third issue is, in summary, I could find no compelling reason not to support Singulair becoming an OTC product and believe that it might help the many allergy sufferers who wish to self-treat. Having Singulair available OTC will give these patients access to a new class of non-sedating, effective allergy treatments other

than nasal triamcinolone, oral antihistamines, and oral decongestants.

So as a clinician, my analysis supports the application. I see no compelling reason not to approve it. And I think it should be approved. And I think it will be useful for many patients. So thank you very much for allowing me to provide this clinical perspective.

DR. PARKER: Thank you. Speaker number 5?

DR. CAROME: Good afternoon. I'm Dr. Mike Carome, director of Public Citizen's Health Research Group, testifying on behalf of myself and Dr. Sid Wolfe. We have no financial conflicts of interest. We strongly oppose approval of OTC montelukast because relative to existing FDA approved over-the-counter products for allergic rhinitis, the drug offers marginal clinical benefit relative to placebo and generally appears to have inferior effectiveness compared to existing over-the-counter products. And two, it poses a significantly greater risk both to patients who meet the proposed indication and those likely to

use the drug off label.

The table shown here shows that montelukast is no better, and perhaps worse, than loratadine for treating seasonal allergic rhinitis. Compared to placebo, it showed marginal benefit in phase 2 and phase 3 studies. One study, 246, in perennial allergic rhinitis patients revealed that montelukast was no better than placebo, whereas cetirizine was statistically better in improving daytime nasal symptom scores. A second study, 265, showed that montelukast had a greater effect than placebo, but the difference was not clinically meaningful.

In assessing efficacy of montelukast, FDA noted, intranasal of corticosteroids are recommended as first-line therapy for moderate to severe allergic rhinitis with second generation oral antihistamines preferred for treatment of mild or allergic rhinitis, owing to their safety and ease of use. There are not data demonstrating that leukotriene receptor antagonists combined with either antihistamines or corticosteroids reduce

symptom scores more than antihistamines or corticosteroids alone.

Montelukast poses many serious risks that are unique compared to other over-the-counter allergic rhinitis meds. Most concerning are the neuropsychiatric adverse events. Pharmacovigilance data and numerous reports in the medical literature demonstrate associations with this drug and neuropsychiatric listed on this slide in adults, adolescents, and children.

The current drug label for prescription montelukast discusses this association in warnings and precautions noted here. The clinical details of some postmarketing reports involving Singulair appear consistent with a drug-induced effect. Patients and prescribers should be alert for these events. Prescribers should carefully evaluate the risks and benefits of continuing treatment with the drug if such events occur.

Many reports of neuropsychiatric associated with montelukast exposure provide compelling evidence of a causal link to the drug. For

example, Cereza in 2012 reported data gathered from 24 reports of nightmares in 17 children and 7 adults; 14 had other psychiatric symptoms. In all cases, montelukast was the only suspect drug. In 18 cases, the nightmares appeared within the first day or first week of exposure. The nightmares resolved with discontinuation of the drug in 21 cases. And for 3 patients reexposed to the drug after nightmares had resolved, in all three, nightmares recurred.

Also, Bygdell in 2012 presented data on spontaneous reports of psychiatric adverse events in children in the Swedish Drug Information System from 2001 to '10. Of 744 such events, montelukast was the most frequently suspect drug after exclusion of vaccines and involved 92 cases. The most common reactions are nightmares, aggressiveness, sleep disorder, and others listed here.

Ninety-three percent had a positive dechallenge and 38 percent had a positive rechallenge. Also of note, the FDA reviewers

highlighted 10 sample suicide case reports for which the behavior changes appeared to be correlated with use of the drug or the suicide occurs within a short time after starting or restarting the drug.

The potential for inappropriate and potentially dangerous off-label use of over-the-counter montelukast by adolescents and children, and by patients with asthma, is high for several reasons: 1) the potential target population for the drug is huge; 2) there is considerable overlap between allergic rhinitis and asthma; 3) consumer studies indicated that many consumers, particularly those with low literacy and adolescents, misunderstood for whom the drug is intended; and 4) if approved, this would be the only available over-the-counter product also approved by the FDA in prescription form for treating asthma.

Combining these factors with the expected wave of aggressive, direct-to-consumer advertising by Merck will undoubtedly lead to off-label use by many patients, including asthmatics and children.

The danger was highlighted by the FDA, noting that examples of use of the prescription product have occurred in patients with asthma and that some of these may have been associated with fatal outcome. Other serious risks are listed here, and I note that potential interaction has been shown with grapefruit juice.

In conclusion, to our knowledge, no other country has approved over-the-counter montelukast, and the FDA should not make the mistake of having the U.S. be the first to do so. We urge the committee to recommend against approval of this drug because there is no evidence that it is more effective than, or even as effective as, existing over-the-counter products. There is no evidence that it provides any additional benefit combined with other over-the-counter products. And the risk profile clearly is worse than existing over-the-counter products for allergic rhinitis. Thank you.

DR. PARKER: Thank you. Speaker number 6?

MS. TURNER: Good afternoon. My name is

Kimberly Turner. I represent Allergy and Asthma Network Mothers of Asthmatics. We have no financial relationship with the sponsor.

Allergy and Asthma Network, AANMA, is a leading grassroots patient advocacy organization dedicated to ending the needless death and suffering due to asthma, allergies, and related conditions. During the past 29 years, AANMA has worked alongside hundreds of thousands of patients, caregivers, and healthcare professionals to achieve optimal health outcomes.

We appreciate this opportunity to provide comments to the Nonprescription Drugs Advisory Committee regarding over-the-counter montelukast for temporary relief of symptoms due to hay fever and other respiratory allergies in adults.

We have significant concerns with the approval of montelukast for the temporary relief of symptoms due to hay fever and other respiratory allergies in adults. First and foremost is the potential for off-label use in the OTC setting. According to the FDA, "OTC drugs are defined as

drugs that are safe and effective for use by the general public without seeking treatment by a healthcare professional."

Montelukast, brand name Singulair, was introduced in 1998 for the prophylaxis and chronic treatment of asthma in adults and pediatric patients. It has consistently made the top ten of most prescribed and costliest prescriptions. In fact, in 2010, worldwide sales of Singulair were $5 billion, 3.3 billion in the U.S., nearly 11 percent of Merck's total revenue. Since the patent expired in 2012, generic introduction has significantly impact Merck's profitability.

Merck now stands before the FDA asserting Singulair should be over the counter as an indication for hay fever and respiratory allergies in adults only. The truth is, however, patients will not discern a safety difference between 4- 5- or 10-milligram tablets, nor will they understand the OTC version is only appropriate for hay fever and respiratory allergies in adults. They will simply see a trusted product taken for asthma on

the pharmacy shelves and assume they consume it without the oversight of a healthcare professional.

Asthma, however, is a chronic disease affecting more than 26 million Americans. Every day, 9 to 10 people die from asthma here in the United States. To many, these are nameless statistics, but to us they are family members like Christopher Ledford, Krissy Taylor, and my own 10-year-old daughter, Kaitlin [ph]. Moreover, the data clearly demonstrates mortalities are equally distributed across mild, moderate, and severe asthmatics, thus reinforcing the variability and lack of predictability of the chronic disease.

Asthma is not an easy disease to self-diagnose or self-treat, and, therefore, it's inappropriate for consideration in the OTC setting. Singulair's proposed OTC label actually incorporates forewarnings for patients to see a healthcare professional and attempts to address the potential of off-use, albeit unsuccessfully, according to the label comprehension studies.

In its submission to the FDA, the

manufacturer clearly states, "Because the conditions share a common pathophysiology, there is considerable overlap between allergic rhinitis and asthma within 10 to 40 percent of patients with allergic rhinitis having coexisting asthma."

Conversely, up to 90 percent of asthmatics have concomitant allergic rhinitis. Thus, overlapping the fact that montelukast is indicated for and predominantly prescribed for asthma raises the question as to whether consumers will use this product to treat asthma symptoms. And if such, use would lead to adverse asthma outcomes due to stopping other asthma medications or failing to follow up with health providers for asthma.

Second, we have additional safety concerns due to reported neuropsychiatric events. In 2008, the FDA initiated a safety review of drugs that act via the leukotriene pathway to cause neuropsychiatric events including agitation and aggressive behavior. At Allergy and Asthma Network Mothers of Asthmatics, we have spoken with numerous families who share their horror stories of how this

product altered their loved one's lives and behaviors negatively.

AANMA strongly recommends additional OTC montelukast labeling comprehension studies to be completed to limit the confusion and potential of off-label use. Second, all OTC products to treat hay fever should include a strong warning label on correct use and recommendations to seek professional medical help if symptoms are not controlled with the correct use of OTC product.

We stand before you today representing one thing, patients' best interest. We seek no commercial benefit nor have further ulterior motives. We hope our comments will help the committee make their decisions. Thank you.

DR. PARKER: Thank you. Speaker 7?

(No response.)

DR. PARKER: Are you speaker 8?

MS. JUROVITZKI: Good afternoon. I am Yana Jurovitzki, director of public affairs for Blue Ribbon Advocacy Alliance. I have no financial disclosures to report.

Blue Ribbon Advocacy Alliance is a national grassroots advocacy organization that unites the voices of men and women around the common goal of improving the health of men, their families, and the policies that affect them. Our goals are to educate men, women, and the general public about men's health issues;

Increase availability of resources, education, and awareness tools for men, women, and families affected by men's health issues to advocate for increased public and private funding for research for men's health issues, as well as greater access to screening, treatment, and services for prostate cancer and other men's health conditions;

Leverage a national network for the exchange of information among men, women, and families affected by men's health issues; and

Promote the dissemination of personal chronicles by men, women, and families affected by men's health issues to and among individuals, policymakers, and the media.

The Consumer Healthcare Products Association's findings in a 2013 survey demonstrated that more consumers readily use allergy relief, over-the-counter medications than other over-the-counter medications. Seventy-four percent of primary care physicians recommended over-the-counter allergy relief of symptoms before recommending a prescription treatment, and that most specialists either had no reservation recommending over-the-counter medications or would encourage patients to read and carefully follow instructions before taking the medication.

Over-the-counter medications provide symptomatic relief for 240 million Americans, where an estimated 60 million would otherwise not seek treatment if these medications were not available without a prescription. Over-the-counter availability allows both insured and uninsured allergy sufferers to avoid the cost of doctor visits, diagnostic tests, and prescription, thus creating a total annual savings of $102 billion.

For every dollar spent on over-the-counter

medications, the healthcare system saves roughly $6 to $7. Allowing patients to access these medications over the counter expectedly improves convenience and expedites symptom relief. The use of over-the-counter medications may contribute to improving patient wellness, treating illness, increasing productivity, reducing work absenteeism, and resulting in fewer unnecessary doctor visits.

Forty-five million Americans suffer from allergies, accounting for 10 million missed workdays each year. And many say that their allergies are worse now than ever before. Allergies are this country's most common yet frequently ignored disease.

Some studies show that men exhibit higher sensitivities to common allergens than women do. And as men's health advocates, we at Blue Ribbon Advocacy Alliance support greater patient access to over-the-counter allergy relief medication such as Singulair. Making Singulair an over-the-counter allergy relief medication for adults is a cause that we are very happy to support. Thank you.

DR. PARKER: Thank you. Speaker number 9?

(No response.)

DR. PARKER: Okay. Speaker number 10? Thank you. Speakers.

MS. MARKLE: My name is Jenna Markle. I founded Parents United for Pharmaceutical Safety and Accountability in 2008 after I discovered my son Zachary's five-year struggle with symptoms of mental illness was actually the result of an adverse reaction to Singulair. One of the reasons Zachary suffered for so long was because his prescribing doctor did not warn me about Singulair's potential side effects. At the age of 8, my son wanted to die because he could no longer tolerate feeling so sad and angry all the time. After stopping Singulair, Zachary tolerated his allergy symptoms without expressing these sentiments.

Joining me is Jan Gilipin, another founding member of Parents United and also parent of a child who experienced side effects. We have been contacted by hundreds of parents whose children,

loved ones, or themselves have suffered with Singulair's side effects.

The nature and seriousness of Singulair's side effects and its primary role as an asthma maintenance medication in adults and children renders Singulair inappropriate for over-the-counter marketing. Over-the-counter availability will compromise consumer safety, outweighing any consumer benefit of being able to purchase Singulair without a prescription to treat allergies. The only party who will benefit is its manufacturer, Merck.

Merck and FDA have already established that treatment with Singulair should involve a physician. Prescribers should carefully evaluate the risks and benefits of continuing treatment with Singulair if psychiatric events occur is something that is listed in the prescribing information. This morning when asked about calculating dosage in children based on weight or on age, Merck's own representative stated that a doctor should determine the dosage taken.

Over-the-counter Singulair would confuse customers and consumers and offer them a false sense of security regarding its safety. I fear it will also influence physicians to disregard the warnings about neuropsychiatric events with Singulair, resulting in misdiagnosis of side effects and possibly treating them as primary illnesses.

Some parents have reported to Parents United extreme difficulty identifying side effects with the assistance of a physician, with some children requiring exams by multiple specialists, undergoing numerous tests, including EKGs, CATs, MRIs, blood tests, accruing thousands of dollars in medical costs. If accurately identifying side effects is this much of a challenge for medical professionals, how can we expect the average consumer to be able to do it?

Churg-Strauss syndrome, which can permanently damage the body's organs and tissues and can be fatal without proper treatment, is challenging for physicians to diagnose due to the

wide range of symptoms and their similarity to those of other disorders. Singulair is associated with a wide variety of side effects which consumers may not link to an allergy medication, especially if side effects do not manifest immediately.

Parents United has received reports that side effects were apparent after days, weeks, months, and sometimes years of use. Delayed onset of neuropsychiatric events in Singulair has also been reported in the medical literature. Today, Merck could not tell us when side effects would manifest.

Parents United shares FDA's, Public Citizen's and AANMA's concerns about over-the-counter Singulair. We also share concerns that Singulair Allergy, if approved, could be used inappropriately, creating a Pandora's box. Subjects understanding directions in a clinical study does not translate into consumers following directions outside the lab. FDA recognizes that patients don't typically follow instructions, and research indicates consumers take over-the-counter

medication instructions less seriously than those of prescription drugs.

Just as there would be nothing to prevent consumers, including minors, from purchasing and using Singulair for self-diagnosed or serious asthma, or giving it to a child of any age for allergies or asthma, OTC status would give consumers with preexisting psychiatric problems unrestricted access to a drug that may exacerbate their symptoms. Because over-the-counter Singulair Allergy may be given to children or taken by children, the experiences of children must be considered when this decision is made.

MS. GILPIN: A simple list of Singulair's neuropsychiatric side effects cannot adequately describe the trauma experienced by those who had adverse reactions to this drug. Here is a list of experiences that have been reported: severe anxiety that interfered with typical child development and experiences, including school; diagnosis of bipolar disorder, depression, or ADHD and treatment with multiple drugs for these conditions, often without

effect; ER and hospital admissions; admissions to psychiatric units and residential facilities; self-injurious behavior; violence against others; diagnoses of seizure and movement disorders; and thousands of dollars spent by families and insurance companies to diagnose and treat side effects.

This trauma happened to children like 15-year-old Cody Miller, who took his own life within weeks of starting Singulair Allergy; and 11-year-old Matt Faraone, who left school because of crippling anxiety; and my own 6-year-old, Jeremy, who lost his ability to make friends, became afraid of everything, and started to lose all interest in life.

Since 2009, Parents United has been receiving inquiries from parents wanting to know more about Singulair's side effects. "How long will these side effects last, and will there be lasting damage? I want my child back." Our children have been changed forever by the trauma they endured while suffering Singulair side

effects.

More investigation of Singulair side effects is desperately needed, but rather than conduct the research to determine the mechanism for neuropsychiatric side effects, which it admits it does not understand, Merck has chosen to invest resources to unleash this drug on an even wider pool of unsuspecting consumers in an effort to increase the profitability of a drug that has already earned billions of dollars while it was still unpatented.

I get hay fever. It's a little annoying. But it does not begin to compare to the horrible mood and mind-altering symptoms that my son and countless others experienced from Singulair. The primary responsibility of the FDA is to ensure the safety of consumers. Please keep Singulair behind the counter, and thank you for listening.

DR. PARKER: Thank you.

The public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience. The committee will now

turn its attention to address the task at hand, careful consideration of data before the committee as well as the public comments. We will now proceed with Dr. Yang's charge to the committee.

Charge to the Committee - Lucie Yang

DR. YANG: Thank you, Dr. Parker.

Over the next few minutes, I will focus on the questions you are asked to consider and try to provide some guidance on the context in which they were written. We come back to the topics for discussion in Dr. Michele's opening remarks and ask you to keep in mind the proposed OTC setting for use. In addition to a discussion of efficacy and safety and risk/benefit profile, we are asking you to discuss the adequacy of the Drug Facts label and consumer package insert.

Before we get to the questions, I want to remind you of the laws governing FDA decisions of approval or non-approval, which are relevant to how we ask you to consider the questions. Of note, these laws apply equally to products for prescription and OTC use, and the standards for

efficacy and safety as set out in the Code of Federal Regulations are the same.

The Code of Federal Regulations, or CFR, states that FDA will approve an application after it determines that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling. The regulation also mentions that there are many kind of drugs that are subject to the statutory standards, and the wide range of uses for these drugs demand flexibility in applying those standards. Thus, FDA's required to exercise scientific judgment.

The aim of this meeting is to get your views and scientific judgment of safety and effectiveness of 10-milligram montelukast for OTC use to help guide our decision-making ability on these issues. Let me now discuss the standards of efficacy and safety.

Efficacy standards are shown in this slide. The language is from a CFR section on refusal to approve an application. One clause to note related

to this meeting is substantial evidence, meaning that efficacy must be certain and without any doubt. The standards for safety are shown on this slide. This language is also from a CFR section on refusal to approve an application.

The regulatory language in these three paragraphs boils down to four safety reasons for non-approval; first, the submission does not have adequate tests to assess safety; second, the product is unsafe; third, the submitted results do not show that the product is safe; and fourth, there is insufficient information in the submission to determine whether or not the product is safe. Note also that all of these safety standards are relative to the labeled use of the product, in this case, for use by the consumer without input from a health professional.

This brings us to the questions. The first question is a discussion of efficacy, including the new ocular indication. The next question is a discussion of safety as related to OTC use. We ask that you include discussion on neuropsychiatric

events, adequacy of proposed labeling regarding neuropsychiatric events, potential for off-label use and consequences of such use, and pediatric use.

The third question is a voting question for safety. We ask you to consider montelukast safety in the context of OTC use and the population for which the product is proposed.

The final discussion question focuses on the proposed Drug Facts label and consumer package insert. Note that these labels are provided to you as appendices in your briefing package.

In the last question, we ask you to bring it all together to balance the scales of safety and efficacy in the proposed OTC allergic rhinitis indication. Note that this question focuses on the nasal indication, and you are not voting on the proposed ocular indication. I turn the podium back to Dr. Parker to open the discussion period. Thank you.

Questions and Committee Discussion

DR. PARKER: Thank you. We will be using an

electronic voting system for the meeting. Once we begin our vote, the buttons will start flashing and will continue to flash even after you entered your vote. You will press the button firmly that corresponds to your vote. If you're unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we'll go around the room -- this is after the items on which we vote -- and we'll ask each individual who voted to state their name and vote into the record. Also, we ask that you state, if you're willing to, the reason why you voted as you did. And we will continue in the same manner until all the questions have been answered or discussed.

So we will begin now. Let me remind you, as you take a look, that there are three items for discussion, and there are two voting items. And we will begin with discussion of item number 1.

Item number 1, discuss the efficacy data for montelukast sodium, including data regarding the relief of ocular allergy symptoms.

So I will ask, as we begin our discussion of that, to have you -- let Ms. Bhatt known that you're interested in getting in the queue for that. And then we will attempt at the end of the discussion to try to capture those points in summary for the FDA. So let's begin with discussion of item number 1.

Dr. D'Agostino?

DR. D'AGOSTINO: If I understand the data correctly and the presentations correctly, the efficacy for the daytime relief of allergies and so forth is substantial, and they already have approval on the Rx level. And the FDA presented -- Erika presented on page 4, slide 7, the data on that, which the daytime nasal symptoms were significant. The effect is small, but it evidently worked in terms of the approval on the prescription.

As far as the ocular, one can argue from a

statistics point of view that they attained the Daytime Nasal Symptom Score significance, so they can march on to look at other things. I'm very bothered by the possibility that they could have looked at a lot of different things, and then found one that seems to work. And I'm still confused in terms of why the sponsor presented five studies, and the FDA was only given three of them.

So I have concerns about that, but I think the direction is certainly correct and expected. Again, very small effect sizes, but there is a consistency going on there.

DR. PARKER: Do we have any others from the committee who want to make comments about efficacy and to also comment specifically about the ocular symptoms in terms of efficacy? Dr. Platts-Mills?

DR. PLATTS-MILLS: I'm slightly confused by the two questions that we have to vote on, and it affects what we discuss at this point. The vote on question 3, has the safety of OTC use of montelukast sodium for relief of allergy symptoms, considering potential off-label use, been

adequately demonstrated? That's that question.

The second voting question -- we only have two voting questions. Is that correct?

(Ms. Bhatt nods affirmatively.)

DR. PLATTS-MILLS: Yes? Is the risk/benefit profile of montelukast sodium supportive of OTC use in adults for nasal indication "temporarily relieves symptoms due to hay fever or other upper respiratory allergies"? We're actually not voting on the ocular symptoms at all. Is that correct? And what is the basis of that decision? I don't understand that.

DR. D'AGOSTINO: Yes. What I was trying to say is that -- and we're splitting that up, that the eye indication is not part of our vote. And I think that's where -- if we had questions in terms of the significance of the data, we would have a bigger discussion. But it's this daytime versus the eye -- the eye is being removed from our final voting. And I just asked Lucie when she came down, and that is, in fact, correct.

DR. PARKER: Thank you for those comments.

And I think this is important for us to be clear as an advisory on exactly -- so I'd like to turn to the FDA to make sure that you-all are clear to us that we have what we will call common understanding between what it is you'd like to hear from us and what will we provide so that we can give you our best advice regarding efficacy and the voting questions. Thank you.

DR. MICHELE: Yes. I believe that you do have a correct understanding. So question 1 is a general efficacy question. The sponsor is asking for a new indication. We're interested in hearing your thoughts on it as far as the ocular symptoms. We also have the question there so that you can discuss efficacy from the perspective of OTC use, so when you vote on the final question of the benefit/risk, you have both portions of those in mind as you're doing your voting.

We have intentionally removed ocular from your vote of the risk/benefit given that we were curious if that had been removed, how you would vote. So we didn't want to color the vote based on

potentially small sample effect sizes for the ocular indication.

DR. PARKER: So my understanding of that -- I'm going to take a little leap here, friends -- is that they are interested in the opinions of the committee regarding our view of efficacy and ocular symptoms, which I believe we've had some comment on already statistically. I believe the term was "statistical march," and perhaps some leaps being made there, if I'm understanding that.

So I think it's important if others on the committee would like to provide any comments or thoughts that they have on efficacy. I think it might be helpful to actually in our minds break it down. And I might even ask that we look at what our advice and thoughts are regarding efficacy with ocular symptoms since that is not something we're voting on. That is something that we can provide feedback on in terms of a discussion.

So I might start with that. And then if there are other comments or thoughts regarding

efficacy more broadly, this would be the time to bring up those comments.

Am I understanding that correctly?

(Dr. Michele nods affirmatively.)

DR. PARKER: And I will offer my own thoughts here, just that I had the same concern about adequacy data to support the ocular symptoms based on what's been presented. And I understand that we are not being asked to vote on that. But were we being asked to vote, I would certainly bring up my own concerns about whether or not there's adequate data. I don't believe there is at this point to be able to say that. So I'm going to go all the way out on that one.

The other comment I would make regarding the efficacy, though understanding what has been approved for prescription use, I also have concerns about how that lines up with current clinical guidelines and believe that that's a really important consideration and have heard some other comments along those lines that there's actually not a lot of data about improved efficacy on top of

currently recommended clinical guidelines for the conditions for which it's being asked for approval.

So I'll put those comments on the record. If there are others who'd like to say anything? Yes?

DR. ROUMIE: Christianne Roumie. So one of the concerns I think that was brought up earlier was the clinical threshold of this change of .1 in the ocular effects. And for the Nasal Symptom Score, we had an active comparator to see the effects of cetirizine or the active comparator to kind of get a sense of a change from baseline.

But I don't see any active comparator in an of the ocular symptoms. It was really only the comparison to placebo. And I think for us to determine what is a clinically significant change, it would be nice to have an active comparator to be able to hold that to the same standard, for the ocular symptoms, because right now a change in the eye symptom score of minus 0.1 means nothing to me on a scale of zero to 4. So it would be nice to have seen the change for the active comparator.

DR. PARKER: Dr. Platts-Mills?

DR. PLATTS-MILLS: I don't think I quite realized that question 5 of the vote has clearly taken out the ocular indication, and that's not in there. And that's clear now. I was just surprised that that decision had clearly been made by the FDA firmly before we saw this.

I think that in practice, I think most of us are aware that there are patients who won't take nasal steroids at all, won't take loratadine. Loratadine interferes with thinking in quite a lot of patients. Very few people can write a grant while taking loratadine and that Singulair has a role definitely in nasal symptoms in a proportion of patients. So exactly as we see with asthma, there's a specific role.

I have no sense of that in relation to eye symptoms. And I don't know there are people who've got enough experience with eye symptoms to know -- have a sense that there really is a group of patients where this is the drug of choice, so that I'm not unhappy about the decision that's been

made.

DR. PARKER: Dr. D'Agostino?

DR. D'AGOSTINO: With regard to the positive -- the active comparator, do the regulations say it has to be like an active comparator? Years ago, I wrote a paper, when I was doing a lot of work in the OTC, saying that if you're looking at aspirin or something or an analgesic, you should put aspirin in the study so aspirin beats the placebo. Then you have what I would call downside sensitivity, then does the new drug beat the placebo, so that there's a full package.

But that was not so much regulation as opposed to looking at -- trying to get sense of the data. And am I wrong -- I'm stating a position, but is it sufficient for the drug to beat out the placebo for approval?

DR. MICHELE: Right. So Dr. Yang reviewed the efficacy requirements. There's no requirement in the United States that a product beats an active comparator. It must beat placebo.

DR. PARKER: Dr. Tracy?

DR. TRACY: As we think about these things, in asthma, Singulair really is a stand-alone drug in many cases. But in allergic rhinitis, for most of us -- I'm an allergist, and probably 50 percent of my patients are kids -- I don't know that I've ever used this for anything ocular. And even for the nasal stuff, it's really -- as Dr. Platts-Mills has pointed out in the past, there is probably a subset of individuals who really benefit from it. But from an eye standpoint, this would not be a go-to drug.

DR. PARKER: Dr. Ownby?

DR. OWNBY: Yes. I was just trying to think of what a consumer would say. I'd like to thank the sponsor for providing a mockup of the packaging, and it's very helpful. But if I look at the front of this and it says "24-hour relief of," I will grant nasal congestion, sneezing, runny nose, and itchy nose. Those are all I think well shown. But when it says itchy, watery eyes, I'm not convinced at all by the data that that's a

reliable statement that most consumers would assume, from looking at this packaging, was true.

DR. PARKER: Let me just ask the agency, did you get the information to the -- what you were looking for in that question?

(Dr. Kweder nods affirmatively.)

DR. PARKER: Good. So just to attempt to summarize, regarding the discussion of number one with the efficacy data -- and specifically, this is our discussion about the ocular symptoms -- it sounds as if there's concern statistically, though signals are small and perhaps in the right direction. There's concern, uncertainty, to not convince regarding efficacy with the ocular symptoms. There was also note of the no active comparison and then the comment from the FDA regarding that, and one comment regarding whether or not -- what the clinical meaning is of the differences that were noted.

Have I missed anything from the viewpoint of the advisory? Make sure I represent you well here.

(No response.)

DR. PARKER: Okay. Thank you. That was nice. Let's move on to number 2. Under number 2, we will discuss the safety profile of montelukast sodium for the over-the-counter setting, include discussion on a) neuropsychiatric events; b) adequacy of proposed labeling regarding neuropsychiatric events; c) potential for off-label use and consequences of such use, and pediatric use.

So before we go to the queue for this, let me ask first if there is a need for any clarification specifically related to the question and what we're being asked, so that we're certain that we are answering what -- does anyone have any need for clarification regarding what we're being asked? Otherwise, we'll start with the queue regarding response to this discussion.

Ms. Pledge?

MS. PLEDGE: I have a real concern regarding the neuropsychiatric events. If I had been those parents, I would have been just furious also. But I wonder, too, that if you put it over the counter,

are they going to discuss with a pharmacist some of the potential side effects that could be very dramatic? I think the labeling on the box just regarding that "you experience unexpected changes in behavior, thoughts, or --" well that kind of minimizes, I think, the severity of some of the problems. I really think that minimizes it.

Again, if it's over the counter, I think people are less likely to have a pharmacist review with them the implications of taking this medication or the precautions that they should have. And I remember very distinctly changing pharmacies recently because one of the pharmacies I had gone to before was a big one in a grocery store.

If I was looking around for over the counter, no pharmacist ever came out, or pharmacist helper came out to ask me can I help you with something. But I notice that when I go to a smaller pharmacy, the pharmacist, his eyes open, comes out and says, "Can I help you with something? What are you looking for?" And did you know that

maybe you can't take this because of this other medicine? So I really think that was really important regarding that.

Also -- those were the two bigger things that I had. I think I'm not ready to see it being over the counter for those reasons.

DR. PARKER: Dr. Platts-Mills?

DR. PLATTS-MILLS: Yes. The neuropsychiatric issue raises obviously very significant questions, which are really important. And there is a general problem with the whole issues of rare side effects. And it was very notable that one of the examples we heard about, which was truly awful, the drug was being prescribed by a physician.

There's a very famous example of a child who was given nasal steroids and developed -- became severely Cushingoid and this terrible side effect, but the patient -- had been prescribed by a physician, and the physician had given the aura that the drug was safe. There is just as big a problem -- with rare side effects it is just as big

a problem if a physician prescribes it because the patients have been prescribed by a physician, and therefore, they believe it's safe.

As I said before, if we discuss every side effect that has occurred in 1 in 100,000, we would not be able to function. And you'd frighten patients so much, they'd be unwilling to take any drug. I think that is a general problem in the hall of medicine, that is how you handle very rare side effects or rare side effects. And obviously I don't have a sense of the psychiatric fence, but I've been using Singulair for 10 years, and I haven't seen them. And so I think it's --

DR. PARKER: Dr. Gerhard.

DR. GERHARD: I have two points regarding the neuropsychiatric events. I think, from my perspective, we really just don't know very much about them. From the clinical trials, as Dr., I believe, Towbin pointed out, we really haven't assessed these events in the clinical trials. So the fact that they weren't reported in itself really doesn't mean very much.

Obviously, we're all familiar with the limitations of the adverse event reporting data, so it comes down to the fact we don't know much about it. Whether these events are more problematic if a drug becomes over the counter as in the previous comment, I really don't know. Certainly, it would be a problem if the use would expand greatly if the product goes over the counter. But generally, I think this is really an issue of inadequate information, and this is a very difficult topic to study.

To me, the biggest concern is really when it comes to the issue of the impact of putting Singulair OTC for allergies, what is the impact of this on the treatment of asthma? And that is a different situation for Singulair versus all the other OTC medications and allergy.

We've heard that 8 percent -- or something like this -- of the U.S. population has asthma. Just to take out one of these questions here regarding the consumer comprehension study, "When using this product, if you are currently taking

asthma medications, do not stop taking them." Patients with prior Singulair experience, 94 percent -- had this correct -- the lower confidence bound; 91.2 percent.

Given the severity of asthma and the potential severe consequences of inadequate management of asthma, if only 1 percent or even .1 percent of asthma patients stop taking their medications because Singulair is OTC for allergies, that will cause -- has the potential for significant harm.

Again, this is something that I can't substantiate, but I don't think -- I think it is a significant risk that the data that I have seen from the Label Comprehension Study doesn't really make me -- doesn't relieve me of these concerns. And I think it's very hard to do because it's a situation that's unusual.

DR. PARKER: Thank you. Dr. Roumie?

DR. ROUMIE: So I'm just going to echo a couple of Dr. Gerhard's comments that there does potentially appear to be a signal for the

neuropsychiatric events, but currently the state of, I guess, our understanding is there's really not enough evidence here to either back up the fact that it is truly safe or truly not safe.

My concern is really more in the off-label use for the pediatric population. In the initial Label Comprehension Study for Adolescents, pre-mitigation, 1 out of every 2 15 year olds said it was okay for them to use. So again, we can't assume that those pre-mitigated and post-mitigated, oh, well, I'll ask my parent, who's in the next room, is really what's going to happen. I think you have to look at it and say, this 15 year old looked at the box and said, "Yeah, that's okay for me to use," and that's of more concern to me.

DR. PARKER: Dr. Pruchnicki?

DR. PRUCHNICKI: Thank you. Maria Pruchnicki. As a pharmacist, I would like to respond to some of Ms. Pledge's questions and also just state generally. Certainly when we have drugs in the over-the-counter environment, there are times when pharmacists are available and accessible

and times when they are not, for a variety of reasons; times when patients are willing to engage with you and times when they are not. But there is always going to be that increased access and increased risk, and that is certainly something that we worry about and I think about very often in terms of patients' health literacy and their ability to understand.

I think my greatest concern is the concept of risk and benefit is very challenging for a patient to understand. And when we are asking them to appreciate maybe the subtle differences in effectiveness between one drug over another, that puts really an increased burden on them.

I wonder if the sponsor -- if Merck has thought about are there ways to provide some education or to partner in education so that less of that burden falls to our patients because I know those gaps are really just huge out in practice, and also don't just affect the patients who are seeking the drug over the counter, but also those who are then continuing to take it in a

prescription status.

So if I'm a patient on Singulair with asthma seeing "Don't take this if you have asthma," that could very easily prompt me to stop taking the medication in the absence of advice or not even being willing to initiate a conversation to get that advice due to access or whathaveyou. So I think it really goes both ways.

DR. PARKER: Dr. Kramer?

DR. KRAMER: Yes. I actually would like to make a couple of comments that are sort of a broader or a bigger picture. It seems to me that the issues that we're discussing today about the safety in the OTC environment here really epitomize some fundamental issues and the evolution of drug safety over a number of years.

Actually, my own personal experience is fairly pertinent to these bigger issues. I started with a father who as a pharmacist started practice in 1938 when there were many prescription drugs that you could just prescribe, and I heard the stories of what life was like then.

Before I went into medicine, I was trained and practiced pharmacy and taught pharmacy school. And that was at a time when we had a stringent review of the efficacy of things that had been used for years in over-the-counter use in terms of requiring strict efficacy, and, really, we moved much more to prescription and the learned intermediary.

As we all know, we've moved now to a very big change in our healthcare system, where we want -- as many people have said, there are real benefits of patients having the ability to treat themselves and the availability of OTC products. However, I'm really struck, as I've heard many of the variety of opinions express today, that we have to be very careful in how we speak about this and discern differences.

This isn't just all drugs should be OTC or no drugs should be OTC. This is very specific. And I'd like to make a few comments specific to those general comments about this that we're discussing today.

I think that the physicians among us who talk and who treat patients have to be very careful when we talk about drug safety because there is much greater self-treatment now, and there are much shorter encounters, by necessity, in our practices that really don't allow us to see or hear or explore all the things patients are fully experiencing. And I certainly identify with the frustration of how do you notify everybody of ever side effect and can we really do this in the current environment.

However, we also need to know, therefore, we're not getting as much information about what patients are experiencing. And when a frustrated parent comes in and says what's happening to their [sic] patient, you think, oh, I can't deal with this, I can't interpret this, and you are more likely to reassure and not take seriously things that may be we should take seriously.

Okay. Enough of the general comments. But I think that we should recognize if this drug were available OTC, at the very least, we know that it

will increase the availability and use of this product. And the question is, how much of that is within guidelines and what we want and how much of that is outside of guidelines and could have potential side effects.

Now I'm going to take them one at a time. Neuropsychiatric symptoms, I have to say, I was struck that all the letters we got to review in advance of the meeting were from parents of children who had side effects. Not a single letter we got in advance was supporting this. And then you came to the meeting, and the vast majority at the beginning was all of we need to make this available.

So obviously, a variety of views. But it is striking that among the top ten most common symptoms you see, the cluster of related similar -- insomnia, hallucinations, nightmares, all these things that seemed to fit together, and then the dechallenge/rechallenge, really should give us pause that there may be something there we don't understand.

So the question is, is it in the setting of modest efficacy, which everybody states, reasonable to make this available to this larger group of people with these potential neuropsychiatric effects? And we all need to decide that, but I have some concerns.

From the pediatric standpoint, it is completely illogical, to me, that we should be prescribing this or approving this for 18 year olds and older when it's available Rx for the same indication in 15 to 17 year olds. I don't know how it happened that was the original, but it is now approved in that age group. What is one who's 15 years old to think if this becomes available and it says, but you can't use it. You have to go to your doctor and get the exact same thing, and then you can use it. It just doesn't make sense to me. And I would say, although people have pointed out, there are a lot of drugs that are available OTC and Rx in different dosages. But usually, the OTC is a lower dose, not a higher dose.

So what is the likelihood of the children

taking 10 milligrams? Probably not so unusual. And yes, there's this "safety profile" in small studies, but we don't understand things like potential neuropsychiatric side effects. What's the effect of a 5 year old taking 10 milligrams, long-term? These long-term studies, the personal experience of patients in this application is strikingly short-term use; 250 total patients with a year of experience, and yet all the stories from patient groups -- my son started taking this when he was 3, and five years later, we put together all these things happening. So I'm very concerned about the appropriate dose in pediatrics and how you communicate that.

Finally, I want to say something about the striking reliance on the label to fix all ills in both the sponsor's and the FDA's materials. It's very striking. But if we label it correctly, everything will be fine. So I can't resist but bring up a couple of really pertinent studies that if you are not familiar with, you should become familiar with. And that is -- I'm sure the FDA

knows this.

I have a couple papers in front of me from JAMA. This one is from 2000, I recognize, the Contraindicated Use of Cisapride: The Impact of FDA Regulatory Action. This is the impact of label changes, and the accompanying editorial by Ray Woosley, the father of the CERTs program, who many of you know, the Centers for Education and Research on Therapeutics.

Drug labeling revisions. Guaranteed to fail? Here's a situation where a drug was known to cause a fatal side effect, and it was known what drugs it couldn't be prescribed with. And they tried to get doctors not to co-prescribe this drug, cisapride, with these other drugs that caused QT prolongation, and torsades, and death. After years of trying to change and to label and to warn and to educate, they finally said, you know what? We've got to take it off the market.

Why do we think -- for those of us who have been in practice -- and I was in practice in the mountains of North Carolina. People do not read

labels. They see a name. And the pharmaceutical industry knows this. They call it good will. That is why there are so many Sudafeds on the shelf -- before they took them behind the counter -- because all these drugs with the same name but different ingredients are used because patients choose by the name that's familiar to them. They do not read the details. Talk to most practicing family physicians. They know that patients do not read the label.

So just as a caution there, and I have serious concerns if we think that we can just do this with labeling. And I'll shut up.

DR. PARKER: Dr. Towbin?

DR. TOWBIN: Thank you. I wanted to start by thanking Dr. Gerhard for his concise comments related to neuropsychiatric events. I concur strongly that we really just don't know. The strongest data that one could rely on to determine the presence of these would come from clinical trials. And it's very clear, both from the industry and the FDA side, that the trials were not

constructed in a way that would allow us to get a handle on that.

Unfortunately, in the absence of data, you end up with conflicting testimonials. And that is a very difficult way to make decisions regarding scientific questions. One sort of testimonial is the kinds of things that come through the FAERS system, where we have no idea about the denominators. And we really can't look cases closely, so we don't know quite how to interpret that information.

We also have testimonials from individuals who either practice or take the medicine and say that it's a great thing for them, but those are not scientific. So I think that Dr. Gerhard's comments strike as close to mind as possible. There is no scientific data to assist us in understanding neuropsychiatric events.

There is something suggestive in terms of the dechallenge and rechallenge information that we got. But again, those really are not sufficient, in my opinion. So it makes it difficult moving on

to B to look at the adequacy of the labeling because we really don't know what we're trying to target or work with. We can't really assess how frequent or severe these are.

I think that the comments that Dr. Kramer has made echo my own, that we may be trying to assist ourselves in feeling better about a situation for which we have very limited control. It's hard to say, oh, well, if we change this word or that word. I do think that there's going to be considerable off-label use.

I think that what's going to happen is that this drug, people will hear the name Singulair. They won't see the difference between allergy and prescription. It will be widely used for all ages, for all indications. Neighbors will say, "I tried it. It was good for my child. You should use it for yours." This is the way in which pharmacy is done in the United States, at least nowadays. And I think that there will be widespread pediatric use.

I don't know if that raises much of a

question, but I do have one question. And that is, is there a difference in the FAERS system when an agent moves to an OTC category compared to a prescription category? Could I hear a little bit about the monitoring of adverse events for over-the-counter agents compared to agents that are by prescription? Thank you.

LCDR VOLPE: This is Dr. Volpe here. In the FAERS system, the NDA [inaudible - off mic.] The NDA products are monitored the same way that the NDA prescription products are monitored. We receive reports the same way.

Does that answer your question?

DR. TOWBIN: Yes, it does. And thank you.

RADM KWEDER: This is Sandy Kweder. I want to make sure that we are clear on what she said, is that products that have a new drug application such as this one, where there's a switch from a prescription, they do have the same requirements. What does not have that requirement are some of the older products that are regulated under a monograph. And some of those products would be a

lot of the much more common drugs that are used to treat allergic rhinitis. They don't have that same requirement.

So our ability to compare the data on things like diphenhydramine, pseudoephedrine, some of those kinds of things, is quite different.

DR. TOWBIN: Thank you for that. In fact, I was concerned about that under the monograph because I didn't think that we got that kind of information. So I appreciate your reassuring my memory being good.

DR. PARKER: Ms. Pledge?

MS. PLEDGE: Years ago, when I was working at a mental health center, I got a slew of federally referred clients who were on meth. And several years later, they started taking anything that was pseudoephederine and putting it behind the counter.

I can tell you that right now I work with university students, and some are very devious and clever, especially the drug-seeking ones. They will go into a drugstore and look at something like

this and say, "Dude, you've got to try it." And if it doesn't work on one dose, try two, three pills because this is what will happen next. And most of the counselors will not know, unless they have heard about Singulair, that this is something that could be potentially dangerous for them. Thank you.

DR. PARKER: Dr. Tracy?

DR. TRACY: When I received our briefing packets a few weeks ago, I was a little confused at the whole partial OTC switch. And then I got to question number 2, which talked about the potential for off-label use. I can tell you, this is going to be used a lot, whether it's a 10 year old whose mother wants to save a little bit and they want to cut their pills, or whether they use them as a chewable.

I don't know what the consequences of that is. I'm not sure any of us do. When I raised it earlier, it's something that we just really hadn't thought about. This is not a pill that can be split in two. It's got a film coating on it, so

it's not scored. I don't know how it will affect asthma follow-ups. There's a lot. But I guarantee you this will be used heavily off label.

DR. PARKER: Okay. We're going to move through and hopefully get the next four in fairly quick so that we can move on to the others. I've got Dr. Totman.

DR. TOTMAN: Yes. There are several things I'd like to comment on. One, Dr. Kweder, actually there is a requirement for reporting an adverse event under the monograph drugs, although that's not relevant to what we're talking about here.

RADM KWEDER: It's different.

DR. TOTMAN: Yes, it is different, but all serious reports have to go in.

About label reading, actually, there are studies that show, especially the first time, that consumers purchase over-the-counter drugs. They match more often by symptoms. They're looking for a product that will treat the symptoms they have, and that's what they look at the label for. And there is also reporting of how -- especially the

first time they use the product. They do read the directions, and they do read the warnings. Of course, that's not a hundred percent, but nobody can force people to read labels. But it's important that the information they need is there for them to read.

In the overall consideration of the risk/benefit conversation that we're having, it's important not to lose sight of the true clinical significance --

DR. PARKER: So for risk/benefit, we're going to hold those until we get to risk/benefit.

DR. TOTMAN: Okay.

DR. PARKER: Let's focus very specifically on the safety profile so that we can get through this one.

DR. TOTMAN: Okay.

DR. PARKER: Ms. Simon?

MS. SIMON: I just wondered because it's also used for asthma and supposed to be used over 18 years of age -- and the side effects, will it be kept behind the counter like the antihistamines

that contain decongestants or will it be totally in front of the counter?

DR. MICHELE: Right. So we actually do not have a behind-the-counter class of products in the United States. The behind-the-counter that you see with pseudoephedrine is not something that FDA puts on that product. That's based on drug control laws for abuse potential and has nothing to do with FDA approval. And we actually do not approve products as behind-the-counter per se.

DR. PARKER: I'm going to go back to some people who've already spoken and ask you to make these very focused here. Dr. Ownby?

DR. OWNBY: I'm just struck that the tens of millions of people who are likely to have this drug if it goes over the counter, that we're still admitting that we have very little information on the neuropsychiatric effects. In my own clinical experience, those effects have been subtle in onset. It's not one day you're normal, and the next day you're strikingly different. It's that they come on gradually, and it takes -- that's why

it's so difficult as a clinician to pick these up and say it's time to try stopping this drug to find out is that really what's related to it.

I think that that's my biggest concern. I think the sponsor's made a very sincere effort to address those. The question is whether three months from now you will remember the label that you read today when you first pick up the product.

DR. PARKER: Dr. Platts-Mills?

DR. PLATTS-MILLS: Obviously, in terms of side effects, we're all very well aware of side effects and well aware of side effects over the counter. We have to talk to patients about Zyrtec, which puts people to sleep, the direct comparator to this drug; Zyrtec, which actually is major soporific.

Loratadine, which is at 10 milligrams, but if you take where the company wants to market at 20 milligrams, at 20 milligrams, it's sedating, and they were not allowed to market 20 milligrams as a non-sedating. Benadryl, which is chaotic and psychotic, many patients feel completely crazy on

Benadryl. Other people are fast to sleep and very dangerous when driving; and of course, Sudafed, which we worry about all the time with hypertension.

So we live with this world. And to me, the evidence we have already on montelukast is less than any of those. And as an adult physician, I have not seen these neuropsychiatric effects at all. And in terms of the off-label use, we have students purchasing Ritalin off their neighbor and grinding it up and sniffing it. So the world is very chaotic. This does not have a potential for abuse of that kind.

DR. PARKER: Dr. D'Agostino?

DR. D'AGOSTINO: My comments are very similar. I'm worried about the off-label use, the asthma ratio, how much we really know about the psychological effects and so forth. So putting it over the counter I think does open up a fair amount of concern.

DR. PARKER: Dr. Kramer?

DR. KRAMER: I just want to emphasize, my

greatest concern is on C, the potential for off-label use with asthmatics using this off label. Even if a very small number of asthmatics try to avoid the cost of the physician's visit and start using -- when they realize that Singulair is the same drug that is prescribed for asthma, using it and stopping a controller medication, and having a very serious or fatal consequence, is my greatest concern about this OTC switch.

DR. PARKER: My greatest challenge as a chair is to be able to summarize what you said. So I want to just share with you a quick view of my notes and ask all of my colleagues here to take nothing personally for whatever I missed. But if I missed what you consider the hill you want to stand on, I will allow you to add that hill. Otherwise, we're going to move forward.

So here we go. Here is the Parker attempt regarding the question at hand here. First, with the neuropsychiatric events, looking at safety profile, there was note that in the absence of adequate, clinical trials, "We don't know." That

is very different than we know, yes, or we don't know, no. We don't know. That is what I heard. There is concern regarding also that there may be signals, and that the onset of these neuropsychiatric events is most likely gradual and occurring over time, and we just don't know.

Regarding the adequacy of a proposed label regarding that, we are not good likewise at communicating. We don't know. So thus, to turn to the label and ask it to do something we're not very good at doing anyway is a tall task at best. And there is concern about the ability of asking the label to explain something that is that difficult to be able to communicate in general.

Regarding the potential for off-label use and the consequences of such use, first I heard that, yes, with over-the-counter availability, there will be more use. And with that come concerns regarding specifically asthma and the use of the medication in the population -- as I've heard them referred to, of asthma sufferers -- and also to off-label use among adolescents and the

pediatric population.

There was also mention that this will not currently be behind the counter or requesting any discussion with pharmacy or anything else in the way it's currently being viewed, but that was discussed.

We also noted the evolution, in general, that this poses us to ponder regarding drug safety in the over-the-counter setting over years. The complexity, it's harder, more difficult. There are more options. There's a whole lot more for consumers and the average American to be able to need to understand and navigate. There's a greater need to know to do as more options are available and as information is increasingly complex and presented to people in multiple forms of media.

The reliance on the label to fix that is an area of concern to many. And there was also note that the ability of the public, of the average American, and probably even many in the room, to understand and know what an active ingredient is and how that compares and relates to active

ingredients of products that people are already taking, is, again, a tall task to expect people to be able to navigate and do.

So those are the concerns that I heard discussed. Let me asked the FDA if you felt like you got the information you need from the advisory regarding a discussion of this.

It looks like we got one more.

RADM KWEDER: Yes. One other things that -- a great focus of the discussion, the neuropsychiatric events talked about certainly the unknowns. But one of the things that no one mentioned, and I'd like to hear if anyone has comments on this, is if you look back to the history of awareness of these events -- and I think it was on somebody's slide -- the drug was first marketed in 1998. Between 1998 and 2007, there were one, two, three, four reports of suicide; one suicidal behavior, really single digits.

When the initial drug safety communication by FDA came out in 2008, you see a spike, huge spike, that is on -- and this is in suicide related

things and neuropsychiatric events in general, so focusing on the serious ones. And no one commented on that. We've seen this before, and I just would -- I'm just surprised that no one mentioned that and if there's a reason.

Is that because people think that the evidence for there being a significant concern is evident on its face or what you think the role of that -- was it that suddenly everybody understood and now, aha, we see it? Can you -- sure. Go ahead.

DR. TOWBIN: Kenneth Towbin. I don't mind trying a hand at that. Actually, historically, it's quite interesting to me because this would parallel in time very closely the concern that was raised about the selective serotonin reuptake inhibitors having a signal for these kinds of agitation, aggression, suicidal ideation, changes in behavior, that really were not brought to awareness to physicians and the consumer community until things were sort of dug out.

I think consciousness was raised that there,

in fact, might be these kinds of signals in agents that were not necessarily used for psychiatric purposes. We began to see more and more concern about anticonvulsants and a whole raft of other agents. And I think that timing really falls well within that zeitgeist.

I think the response, then, is advertising works. And I think that this a kind of advertising that when you send letters to physicians and indicate to the wider community that there may be a signal, that people respond by saying, yes, we think there's a signal. Now that may be a true positive or a false positive signal. Increased awareness does not always mean that the attribution is correct. But I do think that this peak, to me, was a response to people being aware and thinking about it. And then, of course, over time, memory degrades and there's less awareness.

I think if one were to go into the community this week or next week and poll physicians about the risk of neuropsychiatric events with montelukast, I think you would find that many would

not know that neuropsychiatric risks have been inserted into the label and that physicians should be aware of them. I may be wrong about that, but that's just my guess.

DR. PARKER: There are a couple of others. Dr. Gerhard, did you have your hand up on this? No. Yes.

DR. GERHARD: I would say regarding the spike that we don't know from this data. But it's very likely to have a direct consequence of the publicity and the initial warning. However, that doesn't mean that there isn't a real problem. So it doesn't change my main assessment, which is we don't know.

DR. PARKER: Dr. Gudas?

DR. GUDAS: Lorraine Gudas. I'd like to say that the neuropsychiatric symptoms are actually quite common in society. So when this is publicized, it seems obvious to me that people will respond to that, and they think -- it's very easy for -- there are lots of studies with medical students, where if you suggest that they'll have a

symptom, they will.

So I think that spike is related to the publicity. You can go on the internet now and find all kinds of things, and people start thinking that they have these diseases or side effects. So I think the spike is related to that, again, whether there's actually a signal. I don't see much signal because I think that even though the clinical trials were designed to assess neuropsychiatric symptoms, if there were a big signal, they would have picked that up. So I don't really see much of a signal.

AUDIENCE MEMBER: May I interrupt the committee on that --

DR. PARKER: No. I regret to tell you that at this point, we're not able to take any more deliberations from the audience. Thank you, though.

Dr. Platts-Mills?

DR. PLATTS-MILLS: Yes. The data -- I mean, the level of 1 in 6 million, or whatever it is, is extraordinarily low and clearly much lower than the

national average for suicide. I'm just thinking that the rate in our county is about one per year in the schools, of suicide. So even 68 in 7 million is probably hardly even elevated. I don't know that.

But a much more serious concern is this what you just mentioned, that is the issue that when a suicide occurs, as parents, we're terrified that it will pick up a rate that other children will follow. So I think that there is a real possibility that will suggest an epidemic created or invented. It's impossible to tell. But as you say, it's not clear there's a signal. I remember reviewing it all at the time, and it wasn't clear there was a signal.

DR. PARKER: We have one more very brief comment on this.

DR. KRAMER: I just think we need to be cautious and understand the postmarketing reporting of safety events. We all know how few physicians ever fill out a MedWatch form. And I think for -- although it's certainly the case that if you

say you might have something, people can imagine they might, it's also true that with subtle, slowly developing things and things that are consistent with teenage experiences and behavioral things, it could be very difficult to raise something and associate it with a drug.

I would like to make one specific suggestion that I might have brought up later, but it's very important. Has the FDA considered doing a study in the Mini-Sentinel system for neuropsychiatric side effects? This drug is used extensively and should be available in the electronic health records and the systems that are participating. You have 150 million lives covered in Mini-Sentinel. Maybe that could be a way to get some data.

DR. PARKER: Thank you. Oh, I'm sorry. Thank you.

DR. STAFFA: My name is Judy Staffa. I direct one of the divisions of epidemiology at FDA in CDER. With regard to Mini-Sentinel, although Mini-Sentinel has a lot of value to us for trying to look at and quantify signals, given the

difficulty with picking up these signals in what is largely a claims-based system, I don't think it's feasible at this point. We've actually thought about that, and as you saw from some of the studies that were already done, it's very challenging to study these in data systems where you don't have more detailed information about the outcomes. So I don't think we would be able to learn much from that.

DR. PARKER: Okay. So what we're going to do is move on to our first vote, which is question number 3. And then at the conclusion of this, we'll take a short break, and then we'll come back to the final two items that we've been asked to provide input on.

Number 3 is a vote. I'll read it, and then I will ask if anyone on the advisory has specific questions of clarity related to the question that you need answered before you vote, and then we will vote. And then we will go around, and when you put on to record what your vote was, I'll ask for you to provide a comment about why you voted the day

you did, if you're willing to.

So the question that has been put before us, has the safety of OTC use of montelukast sodium for relief of allergy symptoms, considering potential off-label use, been adequately demonstrated? There is a note below. And specifically for those who vote no, we'll be asking for you to comment on what further data you fill should be obtained.

So let me ask if there are members of the advisory that need clarity on the question itself before you render your vote on that.

(No response.)

DR. PARKER: That's nice.

(Laughter.)

DR. PARKER: For the voting, let's see, it's blinking. And you're going to -- as I remember, you're going to hold it down for 3 seconds or something like that, a few seconds. And then it's going to stop blinking. And then we'll get the records of those, and then we'll go around with that.

So question number 3 is up here before you.

Thank you. If you will cast your vote now. It actually will not stop blinking until they've been counted, so you don't have to hold it forever.

(Vote taken.)

MS. BHATT: The voting results, we have yes, 4; no, 11; abstain, zero; nonvoting, zero.

DR. PARKER: Dr. Tracy, if you'll be so kind, we'll start with you, and we will go around. And we will ask you to state your name, state how you voted, and then to provide your comment.

DR. TRACY: Thank you for starting with me.

(Laughter.)

DR. TRACY: Jim Tracy. I voted no. It's really the off-label use that really caught my attention. The neuropsychiatric stuff that we don't know about I think it's important, but it was really the off-label use that skewed me.

DR. STONE: Kelly Stone. I also voted no. And I agree with Dr. Tracy that major concerns are off-label use as well as the uncertainty with neuropsychiatric events. So transitioning to over the counter doesn't -- the safety is not there for

me.

MS. SIMON: Tish Simon. I voted yes because I felt it was already proved when they got the approval for prescription.

DR. TOWBIN: Kenneth Towbin. I voted no. I think that, for me, the issue of whether safety has been demonstrated was just too tall a hurdle to clear. I would really like to see prospective placebo-controlled trial data that looks specifically at these kinds of side effects in order to be reassured about what the signal is.

I think there certainly will be off-label use and pediatric use. It's not as if this drug will not be available to people. In fact, it's quite available. It just won't be available unless there's a physician that's attached to it who has some responsibility for monitoring those effects along with an individual or an adolescent.

DR. PLATTS-MILLS: Tom Platts-Mills. I voted yes because I think while the experience is unequivocal, this has been used in millions and millions of patients. And the signal, signals have

not developed at any serious level. There are very rare side effects, but I am not impressed that the risk of those over the counter are any greater with very real side effects than they are in the hands of physicians. That's an over-exaggeration of what physicians do.

DR. OWNBY: Dennis Ownby. I voted no. I am concerned about the use for non-indications as it goes over the counter, especially in children with asthma. And I think that has a lot of potential. Also, I'm hung up admittedly a little bit on the word "demonstrated" because I still think we have a lot of questions about the neuropsychiatric effects.

DR. GERHARD: Tobias Gerhard. I voted no. I stated my concerns before. I'm not quite sure -- since my primary concern, really, is the off-label use for asthma, pediatric asthma particularly, I'm not quite sure what additional data could be provided to alleviate that concern, because I think short of doing the experiment of putting an OTC, I'm not sure that label

comprehension studies or things like that will really get at the true behavior after a partial OTC switch.

DR. ROUMIE: Christianne Roumie. I voted no for many of the reasons that have already been brought up, predominantly concerning insufficient evidence and use in -- in off-label use.

DR. PRUCHNICKI: Maria Pruchnicki. I voted yes. I don't think that the data that we've received from postmarketing, limited as it is, has substantially changed the safety profile of when the drug was initially approved.

I do think in terms of what further data should be obtained, given the seriousness of these admittedly very rare side effects, it would be nice if we could establish some sort of a registry system to try to collect some of this data prospectively since it is a fairly widely used drug. I don't think this will be an isolated incident. We'll have more examples of drugs like this, where we do need to get more data from its real use and practice.

DR. PARKER: Ruth Parker. I voted no because of concerns with off-label use, again, especially among asthma patients and pediatric asthma, and also for the neuropsychiatric signals and the issues related to don't know. I feel that clinical trials, case controlled, are really needed and echo those comments.

DR. KRAMER: This is Judith Kramer. I voted no, and I think I've already expressed my greatest concern was the off-label use, in particular for asthma. In terms of what should be done, I'd like to separate that into two different things.

From the neuropsychiatric standpoint, I think even as a prescription drug, I agree with Dr. Towbin that we really do need to consider doing trials to understand this better. Even though it will be difficult, I think it's important enough to consider seriously.

The second thing about what data would need to be obtained to assure us that we could put this over the counter, if we really believe that self-treatment of asthma is not reasonable, I

really question whether that is a reasonable question to say. Maybe it shouldn't be over the counter given that it is predominantly a treatment for asthma and will likely lead to self-treatment of asthma and probably discontinuation of critical life-saving drugs.

MS. PLEDGE: I'm Estela Pledge, and I'm voting no because one of the things that really caught my attention is the fact that the neuropsychiatric symptoms can be subtle and therefore can take quite a bit of time to find out that perhaps it was Singulair. Number two, I don't think the labeling conveys enough of the dramatic symptoms a person can have with behavioral changes or other kinds of changes in their thoughts and moods. And number three, because I know my clients will use this. Thank you.

DR. GUDAS: Lorraine Gudas. I voted yes. I think the company has data on thousands and thousands of patients. I don't think more clinical trials are necessary. As I said a few minutes ago, neuropsychiatric symptoms are very common in our

society, and I don't see a signal there. I think this committee has to be very careful to evaluate the science and not be moved by adverse event reports, which are not scientific. We don't know anything about those patients, what's going on. And I'm a little surprised, actually, that the committee is so influenced by adverse event reports. I don't think -- that's not science. That's not statistics. That's not the way we should be evaluating things.

So I don't think this he said/she said testimonials are the way we should be evaluating things. So I think this committee has to be very careful to use proper methods when we're evaluating our data.

DR. PISARIK: Paul Pisarik. I voted no, primarily for the fact that asthma and allergies are so tightly intertwined, that trying to separate one from the other is going to be very difficult for the patients and clients to figure out. It's going to be hard to separate it out because on this packet it says, "This product is only used for

allergies. Do not use to treat asthma." It's kind of like saying, well, don't think about zebras. Well, what are you thinking about? Zebras.

So if you said don't use it to treat asthma, that's just going to highlight the fact that this can be used to treat asthma, and it will put that thought into people's minds that maybe, hey, maybe I can cut back on my expensive steroid inhaler because this can be used to treat it. The neuropsychiatric side effects, I think that's a concern. But my primary overriding concern is that they're so tightly intertwined.

DR. D'AGOSTINO: Ralph D'Agostino. I voted no. And just a repeat of what we just heard, I'm very concerned about the asthma off-label use and the pediatrics. But in particularly, the asthma, we've had a number of discussions in the past and so forth how important it is to have control of asthma treatment and so forth with a physician. And here, just as we heard a moment ago, people start switching and thinking they know enough and so forth. And we don't have any data. It's really

a question of not having data to know what the impact of that is going to be, except we do know: If you don't treat asthma correctly, that could be very serious.

DR. PARKER: Thank you. A brief summary of what we've heard here, you have the vote count. And the issues that I heard articulated regarding the nos centered mostly around the off-label use in people who have asthma, the pediatric population, and the confluence of the pediatric asthma population; also, the fact that allergies and asthma are intertwined; and concerns regarding the neuropsychiatric, the don't know; and the concerns about safety not being adequately demonstrated; and the need for more trials, perhaps something that shows true behavior and doesn't rely just on the label to demonstrate what happens here.

For the yeses, we did hear mention of the large volume of use and the lack of significant signals given the large volume of use; the suggestion regarding whether or not there could be a registry prospectively, something that doesn't

currently exist. And then we also heard note about a questioning about adverse event reporting and its validity.

With that, I will say let's take 10 minutes, no longer, for a very brief break. And that is so that when we come back, we are on task and we are focused. And we're going to do these last two items in the same good format. Thank you.

(Whereupon, a recess was taken.)

DR. PARKER: Let me explain what we're going to do here for the next couple of minutes.

(Music playing.)

Clarifying Questions (continued)

DR. PARKER: That's even better. I wonder if we can put in a request. The request line is open.

The sponsor this morning was under the impression, because we had some questions at the time they presented, that we would call upon them again to answer a few of the items that were raised by the committee, where we asked for clarification. And they prepared to respond to us regarding the

issues that were raised, and we need to hear them out on that.

So we're going to hear for a few minutes briefly here as they respond to a couple of specific comments/questions that were raised by members of the committee. They had thought that we would call on them sooner, and I apologize that we didn't do that earlier. We moved forward. But at this time, I think it's important that we hear them out as they respond to a couple of specific concerns that were raised by the committee. So we'll turn to them for a few minutes here.

DR. HEMWALL: Thank you, Dr. Parker. Yes. It was a little bit frustrating for us. I'm sorry. We brought some people here who can provide some additional context to the thinking, and these are all really good discussions. And we've thought about them extremely carefully.

So I want to first introduce Dr. Bruce Bender, who will address some of the discussions that have been had around the neuropsychiatric adverse events. And I'll follow that with

Dr. Allan Luskin, who has thought very carefully about this off-label use for asthma situation.

DR. BENDER: Hello, everyone. My name is Bruce Bender. I'm a pediatric neuropsychologist from National Jewish Health and the University of Colorado. And I promise to stay within my two minutes. But I want to comment on neuropsychiatric side effects. A lot of questions, a lot of discussion this morning and I thought some elements of confusion. Absent from the discussion but very important, I think, is the background rates of neuropsychiatric disorders and particularly mood disorders in this population. That didn't get discussed.

We know from very large studies that adults with allergic rhinitis are twice as likely to have depression; that adolescents with asthma are also twice as likely to have depression. And suicide attempts occur twice as often in adolescents with asthma as they do in the general population. So the incident rate or the background rate is very high, which makes it further difficult to interpret

the anecdotal postmarketing reports.

When I look at the preponderance of evidence and I think about the scientific evidence, it tells me, when I look at the clinical trial data, the epidemiological data, even though it's imperfect -- there's quite a bit of it there -- the absence of any reasonable mechanism, any hypothesized mechanism for how you get from that molecule to serious psychiatric disorders, it's not there. And the preponderance of evidence reaffirms and reassures me that montelukast is a safe medicine. And if there are lingering concerns, those are addressed by the label. Thank you.

DR. PARKER: Thank you.

DR. LUSKIN: I'm Dr. Allan Luskin, currently of University of Wisconsin in Madison, Wisconsin. And I was the initial head of patient and public education for the NIH's National Asthma Education Prevention Program.

There has been a lot of concern and I think appropriate concern about off-label use, that off-label use is something that we have to think

about; we have to be concerned about. But the real question, the nugget that we need to take away is, if there is off-label use, is there a concern for harm? And I think the answer is no, that there is nothing to suggest that patients will stop taking their other asthma medicine. There is nothing to suggest that they will use their rescue inhaler. And there's nothing to suggest that they will sever their relationship with their asthma care clinician, whoever that might be.

If we accept the worst case scenario -- and I heard concerns about worst case scenario that someone might die, that that study actually was done by the ACRN group, the Asthma Care Research Network, of the NIH. And they took people who were well controlled on inhaled corticosteroids and several active arms, including one arm that was switched to montelukast.

While control in general was not as robust, that there was no increase in bursts of corticosteroids, no increase in emergency room visits, no increase in severe asthma attacks. So

there is, to me, no reason to encourage off-label use. We need to try to prevent off-label use. But should the worst-case scenario occur, I don't set a serious increase of harm that might be come from it.

Questions and Committee Discussion (continued)

DR. PARKER: Thank you. You did a really nice job keeping it brief. Thank you very much. And I apologize that we didn't call on you sooner to provide those comments. Thank you. We appreciate that.

So we're going to move right now to discussion of item 4. Item 4 is discuss the proposed Drug Facts label and consumer package insert. So if I could ask if there are members of the advisory who would like to put your name into that queue. Dr. Kramer?

DR. KRAMER: I just realized that one of the things I was confused about when I was reading the background packet didn't get cleared up or maybe I missed it. But I believe the FDA pointed out that the Drug Facts label does not include Churg-

Strauss, a warning about Churg-Strauss. I just wondered if that is still the case and why the sponsor chose not to.

Can we clarify that?

DR. HEMWALL: Churg-Strauss is a vasculitis that's rare and associated with asthma and generally associated with tapering of steroids. So we thought that would be something we wanted to not add to the label to add more information that might distract from the main elements of the label. Having said that, we're very willing to use the exact same language that's in the information leaflet that's available on prescription. It's been out there for a while. And that could easily be added to the package insert as well.

DR. KRAMER: So the sponsor's conclusion is that it's not associated with montelukast, Churg-Strauss? Is that what you just said, that it's only associated with tapering of steroids?

DR. HEMWALL: There's enough information to say you can't categorically say there's never been a case with montelukast alone, but it's generally

associated with severe asthma. If you like, I would invite Dr. Luskin back to the podium to explain that.

DR. KRAMER: That's all right.

DR. PARKER: Okay. I don't think we need to do that, it sounds like. Thank you.

DR. HEMWALL: Like I said, we could put it in the package insert, the same language.

DR. PARKER: Ms. Pledge?

MS. PLEDGE: What I have with the box, the concerns I have, is still, stop use and ask a doctor, I think a little bit more should be said regarding the side effects, that the side effects may be subtle or dramatic. And then on the insert, which goes inside the box, they're usually cellophaned and everything, so I doubt that anybody's going to read this before they buy this, because you just don't open the box.

I don't know. Maybe this should be available -- you know how sometimes the pharmacy puts something up right there just so people can read it before you buy it? Maybe that would be a

solution. I don't know. I don't know that that would change my mind, but it would certainly go in that direction. Thank you.

DR. PARKER: Dr. Platts-Mills?

DR. PLATTS-MILLS: About the Churg-Strauss issue, I think there are very few of us who actually believe that montelukast alone causes Churg-Strauss and that it is absolutely a complication of severe asthma. And virtually none of those patients are on montelukast on their own. So given the enormous number of patients with mild to moderate asthma who are taking montelukast, there's no signal of Churg-Strauss appearing in those cases.

DR. PARKER: I'd like to add my own comment about this. I'm confused, and so I am going to wonder if consumers wouldn't be confused, to see highlighted at the top of this, "This product is only for allergies. Do not use to treat asthma." And then, "When using this product, if you are currently taking asthma medicines," knowing that this could be one of your asthma medicines.

We did not hear -- as I understand it, there were in the label comprehension -- I don't know if it was self-selection or label -- it was in the SOLID, so I guess that's both. But we didn't hear among those who had experience with this product whether or not they were currently using it and whether or not they would think that they could purchase this for their allergies to take in addition to already having been prescribed it for their asthma.

I find that an area of concern given, number one, you could potentially be taking twice as much as you need; number two, if it was going to work, it would have already been working and helping you, and so you're still in need of something else.

So it seems to me that that's an area that needs specific clarity and would need to be tested. I find that an area that is ripe for concern. And I think it also highlights how important it is and how difficult it is to really understand active ingredient. There are studies now that document that it's actually very hard to read, understand,

and know the chemical compounds that are in products and be able to compare them across. And this is one issue that really highlights that, to me. So I have concern about that.

Dr. Stone?

DR. STONE: Just following up on that, under warnings where it says "Do not use to treat asthma," I would add, "unless prescribed by your physician." I would have clarified that.

DR. PARKER: Dr. Tracy?

DR. TRACY: I don't know if it's even necessary. But if it is necessary, could you add something to the effect that, do not chew, do not cut, do not break? It might work on the pediatric misuse issues.

DR. PARKER: Dr. Platts-Mills?

DR. PLATTS-MILLS: Taking your issue, Dr. Parker, and Dr. Pisarik's issue, that is that the two conditions are combined, are so often combined, it may be that one of the outcomes of this meeting is the realization that probably if the drug is to go over the counter, it would be

better to go over the counter with the asthma recommendation as well because it would solve your problem. And there are many of us who would believe that would be a perfectly reasonable step to take it over the counter for asthma, as well as for allergic rhinitis, which would solve your problem of the confusion between the two, which is absolutely real.

I mean, we have patients who take oral steroids. And when you ask them why are you talking oral steroids they say because of my allergies. And then you try and probe, and you discover that they think or know that their allergies precedes their asthma getting worse, and so they take, actually, oral steroids, which has enormously more side effects than this. But I think the problem is that the separation may be a problem because of the confusion, but it's not a safety issue.

DR. PARKER: Are there other comments from the committee members regarding the label, and does the FDA feel they've gotten the information they

need regarding this point of discussion?

(FDA members nod affirmatively.)

DR. PARKER: So to attempt to summarize briefly, there was discussion of Churg-Strauss and its not being included, and whether or not that should be revisited. There was note of perhaps an addition for chewing, cutting, and avoiding doing that due to the impact that could have. There was concern regarding confusion because of the coexistence of as asthma and allergy and whether or not that's adequately presented in the content and something that the average American can understand and act on, and the need to be able to understand the active ingredient, and the fact that this might be an active ingredient that you're also being prescribed for asthma and that being a potential source of confusion.

Okay. With that, we will move on to question number 5. This will be a voting question. I'll read the question, and then I will ask from the members of the advisory if you have any issues or potions related to the question in its clarity

that you would like to have noted and clarified for you before you cast a vote. Then we'll vote. And then we will, again, go around, ask people to state their name, how they voted, and to comment on why they voted that way.

Is the risk/benefit profile of montelukast sodium supportive of OTC use in adults for the nasal indication, "temporarily relieves symptoms due to hay fever or other upper respiratory allergies"? And we'll ask that you vote on that. And if you vote yes, ask if you have additional comments or recommendations for the labeling. And if you vote no, ask for you to comment on what further data you would like to see obtained.

Are there any questions regarding how that is phrased and in need of clarity? Yes, Dr. Tracy and then -- we've got a few. So make sure that Ms. Bhatt has your name. We'll start with Dr. Tracy. Thank you.

DR. TRACY: So is this one of those times where if you voted no before, you can't change your vote?

DR. PARKER: I'm confused on your question. Do you want to change your vote to the first question?

DR. TRACY: No, but we have had new information since that vote. And in the past, if you vote no for effective or safe, when you got to the third question, you had to vote no if you voted for no --

DR. MICHELE: Dr. Tracy, you have been trained well.

(Laughter.)

DR. PARKER: You get a gold star.

DR. TRACY: Can you talk to my wife, please?

(Laughter.)

DR. PLATTS-MILLS: Are you actually telling me you would follow that kind of instruction? That is horrific.

DR. PARKER: Would you like to comment for us? Thank you.

DR. MICHELE: So generally speaking, we ask people to be consistent, logically consistent. But if you have reasons to change and can explain the

logic, then I would say go for it.

DR. PARKER: Okay. So we need to settle that. So hang on. I believe there are other comments. Let's go to Dr. Ownby.

DR. OWNBY: I just had a follow-up on that. I read this as if only adults were going to get it over the counter, which changes how I view this question compared to the earlier question that we voted on.

DR. MICHELE: Yes. So in this question, you're really asked to look at all of the information. The question is phrased based on the stated indication, and it's up to you to decide how much of that you take into account. But generally speaking, we approve products based on their stated indication.

In the OTC world, as in other places, we sometimes consider what would happen if. Although, with that said, it's not necessarily within our purview as FDA to decide on the practice of medicine. Likewise, it's not necessarily within our purview as FDA to decide on what consumers do.

However, we have to think about it from a global public health viewpoint as well.

That's a very hedged statement, but I think you can make your own decisions based on that.

DR. PARKER: Did that help you?

DR. OWNBY: I'm still confused [inaudible - off mic.]

(Laughter.)

DR. PARKER: There are a few others. Dr. Pruchnicki.

DR. PRUCHNICKI: Maria Pruchnicki from Ohio State. I think my thought to share goes along with what Dr. Michele just said. And I'm not sure if this is a voting issue or more of a clinical issue. But in looking at the overall profile, I see this drug is relatively benign. The risks don't seem to be typically very large, but maybe neither does the benefit. And I wonder if putting this in the OTC marketplace actually detracts from the public good because it does give them another option that is maybe least likely to effective for most patients.

So I begin to wonder at what point is it too many choices for them, and what is our role to try to filter that to a greater degree.

DR. PARKER: Dr. Gerhard.

DR. GERHARD: I think I have the same question as Dr. Ownby had. Maybe let me just try to rephrase the answer from Dr Michele. So we should include concerns about off-label use if we have them in this answer. Okay.

DR. PARKER: Thank you for the clarification.

Dr. Platts-Mills?

DR. PLATTS-MILLS: Dr. Michele, I think you've confused something because earlier, you had said that question 5 clearly excluded ocular, and now you said actually we're voting on the indication as proposed.

DR. MICHELE: Yes, we are excluding ocular. Thank you.

DR. PLATTS-MILLS: Thank you.

DR. PARKER: Dr. Towbin?

DR. TOWBIN: My question was answered.

Thank you very much.

DR. PARKER: So I would like to just go back to Dr. Tracy's question that he asked and ask if you would like for us to register if there are people who would like to change their vote based on other -- do not change our vote? I got the answer. I got that loud and clear. Okay.

So we are going to continue to move forward. Thank you. I just wanted to make sure I had clarity on that. We will now move to -- it looks like we have clarity on the question. No other questions from the committee related to that. So we will now cast a vote here, if you will. Thank you. You can press in your --

(Vote taken.)

MS. BHATT: The voting results, yes, 4; no, 11; abstain, zero; no voting, zero.

DR. PARKER: Dr. D'Agostino, I'm going to ask you to go first. We'll go that way around the table, please.

DR. D'AGOSTINO: I was going to suggest that Dr. Tracy might have a much more interesting answer

than I have.

(Laughter.)

DR. D'AGOSTINO: Ralph D'Agostino. I voted no for consistency with my concerns about safety, the risk/benefit, that I am still worried about the asthma and the pediatric off-label use. We did have a little input from the sponsor, but I haven't been able to see that and digest it to change my opinion of the safety issues.

DR. PISARIK: Paul Pisarik. I still voted no for the same reasons. I think it's really hard to disintertwine asthma/allergies. I think for the data that should be obtained, there may be a study where you try using Singulair or montelukast for asthma in the OTC population and see if there are adverse reactions to people not seeing their physician. I mean, that would be the next step.

I think if you're going to make it over the counter, I think it almost has to be for both. And I don't know if there's any safety studies that show that it is safe to use over the counter for asthma.

DR. GUDAS: Dr. Lorraine Gudas. I gave most of my reasons before. But I think this is a safe drug, and I think it will give options to people who for various reasons can't or are uncomfortable using some of the other over-the-counter drugs out there now.

MS. PLEDGE: I'm Estela Pledge. I still voted no for the same reasons I did prior. I still think that there is some information that needs to be highlighted more emphatically, especially on the label.

DR. KRAMER: This is Judith Kramer. I voted no consistent with the reasons I've already given. I'd like to comment, though, in thinking about this, it seems to me that conditions that, according to professional guidelines, seem to have a hierarchy of therapeutic choices that are complex present a challenge to over-the-counter use.

When you think about the complexity of both the asthma guidelines, and even allergic rhinitis in terms of what the recommendations are, if it's mild or moderate and what you can expect if you add

a leukotriene receptor antagonist, I really challenge whether this is reasonable to be over the counter for either of those indications. And I think that's consistent with what Dr. Pruchnicki said, that there may be situations where there are too many choices, and it doesn't add, in a reasonable way, to something that would promote our primary goal of improving the public health.

When I try to give an answer, that's what I'm thinking about. I'm not thinking -- I'm trying to think is the added advantage to patients who need access to drugs greater versus any potential safety issues. We can't think just in terms of sales and product. It has to be the public health initiative.

DR. PARKER: Ruth Parker. I voted no. And I would say the dominant reason that really impacted me was the complexity of decision-making required to be able to understand that this is the right over-the-counter choice in self-selection and in label comprehension. And I think the burden of the task to understand what it is you need to know

to make the wise and good decision for yourself as an average American presents a bigger challenge than that which most of us would be able to navigate.

DR. PRUCHNICKI: Maria Pruchnicki. I'm one of those flippers. I flipped to no for reasons that I stated, and Dr. Parker very eloquently restated. When I think about a comparison to a risk/benefit profile for something like acetaminophen, where the risks are very great but so is the benefit, it seems to me that a third-line drug for a condition like allergic rhinitis, it is very reasonable to ask a patient to engage at some point with a physician for symptoms that are not managed in a more straightforward way.

I think if we're going to ask the patient to be able to extrapolate and infer information, a largely uneducated population, from a Drug Facts label, we can certainly work to increase the expectation that they connect with the physician once a year to get a year's worth of refills. Pharmacists -- our state board, in Ohio at least,

implores us to keep the best interest of the patient in mind. We're not going to let them go without their prescription montelukast over a weekend. We're going to work with those patients to get that refill.

So I think there are mechanisms that we could reinforce to provide access, but I do worry about asking an uneducated public to make very complex medical decisions without more supports in place.

DR. ROUMIE: Christianne Roumie. I voted no. Most of the reasons have already been gone over, but, really, the main driver was that the benefits that I saw for seasonal allergic rhinitis and PAR were modest, and that many of the risks remain unknown.

DR. GERHARD: Tobias Gerhard. I voted no for the reasons stated before. I think these safety concerns, particularly regarding off-label use in asthma outweigh the potential benefits. I know that Dr. Luskin I believe stated that the risks of off-label use would be minimal to

non-existent. I think the answer to that is we really don't know what the impact would be. And that's a risk that I think, yes, I'd be hesitant to take.

DR. OWNBY: Dennis Ownby. I'm the other flipper just so the vote stayed the same in total.

(Laughter.)

DR. OWNBY: Perhaps I misinterpreted Dr. Michele's directive, but I felt that for the stated indicated, there is a very significant potential benefit here compared to a relatively small risk.

DR. PLATTS-MILLS: Tom Platts-Mills. I voted yes because I think the drug is very safe. We've had enormous experience with it, and it works well in a proportion of patients with allergic rhinitis. There is a very large population in the United States who are either uninsured, unable to pay, unable to get transport in whom not having it over the counter is a serious impediment.

There are many, many patients who have had bad experiences with physicians and who don't like

going back to physicians. I think very, very few non-physicians realize how big the population is of people who have bad experienced with physicians and prefer to use pharmacies. And many patients, a lot of the allergic disease world, is prescribed -- not prescribed but actually treated by pharmacists. And the pharmacists probably are just as good as we are at this in relation to allergic rhinitis.

I voted yes.

DR. TOWBIN: Kenneth Towbin. I voted no. I really appreciated Dr. Gudas' comments and folded them into the way that I heard Dr. Gerhard earlier. We really don't know. The science just isn't there, and so I couldn't feel confident that we had demonstrated safety. I think the efficacy of this drug is modest. I think we're generous in saying it's modest. And so, the concerns that Dr. Pruchnicki raised about yet another thing, but in this case one where at least the scientific data suggests that it's only a modest effect.

It's not as if we're voting on whether this drug is available. I understand Dr. Platts-Mills'

comments about access to care, but we're not voting on whether this drug is approved. It is there. It is available for people. And I just wanted to come back to one of the comments that Dr. Bender made related to psychiatric disturbances in this population. Actually, that's an excellent argument for why one needs placebo-controlled trials. Those very high rates actually demand placebo-controlled trials to be done carefully.

This drug was approved I believe in the late '90s. What we've learned about clinical trials in agents has changed substantially, particularly in trying to ascertain neuropsychiatric side effects. We would never construct a trial nowadays the way this was constructed in 1998, which is not to fault the company, but just to say we really don't know. Thank you.

MS. SIMON: I'm Tish Simon. I voted yes. I think it's a safe and effective tool for nasal allergies, but I would like some cautionary labeling for asthmatics.

DR. STONE: Kelly Stone. I voted no for the

reasons already stated. With the safety question, it is an important part of the armamentarium for treating allergic rhinitis. I'm not convinced that the safety data supports putting it over the counter, though.

DR. TRACY: Jim Tracy. I voted no, mostly to be consistent with my past vote and because I follow instructions. That being said, I do believe this drug is generally safe and modestly effective. I think some of the issues that we've raised may be able to be addressed through modification of the labeling.

DR. PARKER: To provide a summary here regarding those who voted no, overall, mostly safe but some remaining concerns regarding off-label use, especially in patients with asthma. Regarding its benefit, its efficacy, modest to modest at best without certainty about the risks, and the complexity of the task and what it takes to understand and be able to make adequate, informed decision-making being above the average American; also the coexistence of -- and a lot of that

relates to the coexistence of asthma and allergies in the population at large

Some comments there about highlighting placebo-controlled trials, neuropsychiatric trials, how they are conducted and how this highlights some issues related to that; and regarding the votes for yes, comments that there is a lot of experience that highlights a safety profile that is good and that the availability over the counter would provide more options, including for those who lack access to healthcare providers or choose not to access healthcare providers, but with a note requesting more cautionary labeling for asthmatics. And I will note that we had two flippers, so it all balanced out there.

Let me ask the FDA if they have any other specific questions that they would like of the advisory.

DR. MICHELE: Yes. So since Dr. Parker has been so incredibly efficient with her use of time, I'd like to just push on one little area to hear more about, which is regarding your concerns for

off-label use. And we heard that quite a lot from the committee, both for pediatrics and for asthmatics.

Could you articulate what outcomes from that off-label use you're particularly concerned about because that may help us as we move forward here.

DR. PARKER: Friends, yes?

DR. GERHARD: Tobias Gerhard. Close to a point that I made before. So my concern is -- and there are multiple concerns about how this could impact self-treatment of asthma by patients, maybe reduced contact with physicians. One of the questions that I highlighted before is when using this product, if you're currently taking asthma medicines, do not stop taking them. Six percent with a bound of about 9.8 percent of the patients with prior Singulair experience get that wrong, and therefore considers stopping current asthma medications based on this.

If that would happen even on 1 percent, half a percent, .1 percent of patients on asthma medications currently, you have significant impact,

significant harm. And I think we just don't know if that's likely to happen, and that's a big risk for a relatively small benefit of having this additional product OTC.

DR. PARKER: I think another point that was brought up earlier just relates to once there is general advertising of the product, the name of the product and its use for asthma in the prescription arena is a source of potential confusion for people who hear it being advertised for one and may have both. And may even have, at times, symptoms of asthma that are made worse by heightened symptoms related to their allergies since the coexistence is there so much.

So trying to be able to sort through this and know what is really going on, and at one point you really need -- because asthma itself can be life threatening -- when you really need to seek medical attention, could this lead to some unintended consequences among people who have asthma in knowing what's going on and what they really need to do about it.

I think that's what the general public hears about at the end of the day, is what do I need to do? What's the best use of my resources, however limited they may be? Do I take this and get it? Do I go? Do I go in? Do I keep taking both if I'm not sure whether or not these words are really the same?

Maybe on my prescription bottle, I don't have the little thing. And montelukast sodium is not written all the way out, and I don't even know if the prescription thing is actually the same as the one I'm talking. Do I keep taking these? What do I do? Does that impact my symptoms? Could this lead to worsening of clinical symptoms? Confusion? Could it lead to unintended consequences in people who have both of these clinical entities at the same time.

I think those are unknowns at this point. When the medication -- one that is so widely used anyway -- hits general advertising -- over which the FDA has no control anyway once it's over the counter and there's no oversight, really, from the

FDA of the marketing that occurs with it -- That goes to the Federal Trade Commission -- how does that end up affecting people who have both these conditions?

Those would be concerns that I would have clinically.

Dr. Ownby, I believe you had some comments.

DR. OWNBY: Well, one of the things we don't usually discuss here that I'm concerned about is the economics of this, that usually when a drug goes over the counter, the price goes down, especially when there are generic products available. And I can see a consumer thinking -- notwithstanding Dr. Luskin's comments -- that I stop my steroid inhaler or whatever, other controller, and just take Singulair without a risk because it's going to be much less expensive than my co-pays or whatever for other medications. And I think that has a lot of ramifications.

The other thing that's related to that is my Gestalt from the literature is that the more

patients fail to see physicians, the greater the likelihood of death from asthma. And I think this is one more thing that may decrease the frequency with which patients see their physician.

DR. PARKER: Dr. Towbin?

DR. TOWBIN: Two things. Kenneth Towbin. In terms of off-label use, Dr. Tracy's comments really resonated with me. I think the greater likelihood is that a parent will see the name of this and will give it to their child when it's the wrong dose, not recognizing that the dose recommendations are very different for younger children. And in fact, the younger the child the greater the risk.

So they'll say, well, you know, I had this allergic rhinitis, and my child's here. He's six. He's got that same kind of runny nose, itchy eyes, so I'll just give him one of mine. We see that very frequently. I don't think there's adequate label information indicating not just that it shouldn't be use, but this dose could be a dangerous dose or an inappropriate dose for that

child. Somewhere I think there has to be some information that this is the wrong dose to give people who are less than 18 or something to that effect.

I wanted also to make the comment about co-pays. It's been actually very interesting to see how this plays out, at least among the population that I see. What's happened for some agents is that the co-pay actually is less than the over-the-counter cost, which insurance will not pick up. And so actually the cost to patients may increase when a drug goes over the counter because their insurance program will no longer pay for it. So I don't believe that access necessarily increases when you convert this way.

DR. PARKER: Dr. Tracy?

DR. TRACY: Yes. I'd like to go back to the name thing just for a second. As I mentioned, I do believe this is basically a safe drug. But I go back to the name. And I recognize name is everything, especially from a trademark and marketing standpoint. But when you think about

Benadryl, it's also marketed as Sominex. Sominex is your sleeping pill; Benadryl is, of course, your antihistamine.

I don't know if that would be a mechanism for improved clarity, so that's the first thing. The second thing is this pill-splitting issue that I raised earlier. About five, or maybe ten years ago -- and I'm certainly not advocating this practice -- we were inundated by a local carrier who was -- so if I wrote this particular cholesterol drug for 40 milligrams, they'd give you -- I'm sorry, for 20 milligrams, they would dispense a 40-milligram tablet and tell you to split it. Well, this is a drug that was never designed to be split, and so they had issues with that. Now, that's been stopped, but I can still sort of imagine how that could happen with this drug.

DR. PARKER: Dr. Platts-Mills?

DR. PLATTS-MILLS: I'm concerned with people talking about the risk in relation to asthma. Adding Singulair to a management regime in asthma

is -- I don't know if it's ever been shown to be a risk. It doesn't have interaction with inhaled steroids, has no problem with aminophylline. It doesn't have a problem with steroids. You can use it, and in a significant proportion of patients, it improves control, and in a significant proportion, it has no effect on control

So the safety issue there is very modest. The safety issue of not going to physicians, there is so many reasons why patients don't go to physicians, but the primary ones are financial. And those are inherent in our society. The issues of persuading Americans to understand things, well, that's the problem the rest of the world has dealt with for many years.

DR. PARKER: Dr. Kramer?

DR. KRAMER: I just want to make sure that we have underlined -- when I said that I was concerned about off-label use in asthma, it wasn't that it would be added to everything else. It was that they would stop the inhaled corticosteroids. And my understanding is that that is not the

evidence-based approach to treatment of asthma. I may be missing something.

DR. PLATTS-MILLS: But we deal with patients who have stopped their steroids all the time because of the expense. The expense is horrific.

DR. KRAMER: But this doesn't fix that problem. Having this available doesn't fix --

DR. PLATTS-MILLS: Well, you can't expect this drug to solve financial problems of another drug. Can you?

DR. PARKER: So let me ask the agency if you got some of the answers you were looking for, and more, or if you would like to -- yes, I'm getting some head nods here.

DR. MICHELE: Yes, that was very helpful. The other thing that I wanted you guys to elaborate on was the question that we asked after the voting question. So if you voted no, what would you suggest that the sponsor do to address your concerns? A few of you mentioned that, but most did not.

DR. PARKER: So this relates to what further

data should be obtained for those who voted no. Do we have members of the advisory who would like to comment on that? Dr. Ownby?

DR. OWNBY: I just have one suggestion. Obviously, suicide -- and thankfully it's rare enough that it takes huge numbers before you can come up with any meaningful information -- and whether some of the amalgamations of HMOs that share data, where you can actually look at clinical information as opposed to just strictly billing information, might be a source of a large enough data set to provide reasonable estimates as opposed to our concern of whether this is real or not.

DR. PLATTS-MILLS: Can I just say a word about the labeling?

DR. PARKER: Yes.

DR. PLATTS-MILLS: Suggesting that you should add anything implies that the font size might get smaller. The font size is already 6 font sizes lower than we're allowed in applying to the NIH for anything.

(Laughter.)

DR. PARKER: Any other specific recommendations regarding that?

(No response.)

Adjournment

DR. PARKER: So with that, we will now adjourn the meeting. Panel members, please remember to drop off your name badge at the registration table on your way out so that they may be recycled. Thank you, everyone, for your attendance and your comments. Be well.

(Whereupon, at 3:58 p.m., the meeting was adjourned.)